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Maternal smoking, alcohol and caffeine use during pregnancy and attention-deficit hyperactivity disorder (ADHD) risk in offspring: Is the association causal?

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Abstract

Observational studies have shown evidence for a positive association between maternal prenatal smoking, alcohol and caffeine consumption and attention-deficit hyperactivity disorder (ADHD) in offspring. However, it is still unclear whether these associations reflect a causal effect or are due to unmeasured and residual confounding. Although evidence from previous studies suggest that the association between maternal prenatal smoking and ADHD is unlikely to be causal, findings are still inconsistent regarding alcohol and caffeine exposure.

In this thesis I used different epidemiological methods and triangulated findings across these methods to find evidence to support a causal effect of maternal prenatal substance use on offspring ADHD risk. The methods used in this thesis included a systematic review, a targeted Phenome-Wide Association Study (PheWAS) approach, a negative control design by using paternal substance use as a negative control, and polygenic risk score analyses. Throughout this thesis I used data from three longitudinal birth cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC), the Generation R (GenR), and the Norwegian Mother, Father and Child Cohort study (MoBa). A triangulation approach illustrated how important it is to apply different methods to infer causality as each method has its own sources of bias, but it is unlikely that different methods are biased in the same way. Therefore, comparing findings from various methods can provide more support on whether a causal relationship exists.

My findings did not provide strong evidence for a causal effect of maternal prenatal substance use on offspring ADHD risk in any of the prenatal exposures. My findings on smoking exposure are in line with existing evidence indicating that the association is explained by genetic confounding. However, my results also suggest that future studies should focus on better phenotyping of ADHD and use bigger samples to detect whether a true causal effect still exists.

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Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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List of Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
ALSPAC	Avon Longitudinal Study of Parents and Children
ARND	Alcohol-related neurodevelopmental disorder
ASD	Autism spectrum disorder
ASRS	Adult ADHD Self-Report Scale
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body mass index
CBCL	Child Behavior Checklist
CCEI	Crown-Crisp Experiential Index
CD	Conduct disorder
CI	Confidence intervals
IQR	Interquartile range
CIDI	Composite International Diagnostic Interview
CIS-R	Revised Clinical Interview Schedule
CNV	Copy number variants
CPRS-R	Revised Conners' Parent Rating Scale
CSE	Certificate of Secondary Education
DAG	Directed acyclic graph
DALY	Disability-adjusted life years
DAWBA	Development And Well-Being Assessment
DISC	Diagnostic Interview Schedule for Children
DNA	Deoxyribonucleic acid
DOHaD	Developmental Origin of Health and Disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPDS	Edinburgh Postnatal Depression Scale
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorder
GB	Great Britain
GCSE	General Certificate of Secondary Education
GenR	Generation R

GSCAN	GWAS and Sequencing Consortium of Alcohol and Nicotine use
GWAS	Genome-wide association study
HRC	Haplotype Reference Consortium
CNG	Centre National de Genotypage
CEU	European descent
IBD	Identity by decent
ICD	International Classification of Disease
ID	Identity
IPIP	International Personality Item Pool
IPSM	Interpersonal Sensitivity Measure
IQ	Intelligence quotient
K-SADS	Schedule for Affective Disorders and Schizophrenia
KSP	Karolinska Scale of Personality
MAF	Minor allele frequency
MAGIC	Missouri Assessment of Genetics Interview for Children
MEC	Medical Ethical Committee
MeSH	Medical subject headings
MoBa	Den norske mor, far og barn-undersøkelsen (Norwegian Mother, Father and child Cohort)
MOOSE	Meta-analyses of observational studies in epidemiology
MR	Mendelian Randomization
MRI	Magnetic resonance imaging
MZ	Monozygotic twins
NHS	National Health Service
NOS	Newcastle-Ottawa Scale
ODD	Oppositional-defiant disorder
OR	Odds ratio
PAE	Prenatal alcohol exposure
PAPA	Preschool Age Psychiatric Assessment
PC	Principal components
PCA	Principal components analysis
PheWAS	Phenome-Wide Association Study
PLIKS	Psychosis-like symptoms
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PROSPERO	International prospective register of systematic reviews
PRS	Polygenic risk score
QC	Quality control
RS-DBD	Rating Scale for Disruptive Behavior Disorders
SCL	Hopkins Symptoms Checklist
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SEM	Structural equation models
SMFQ	Short Mood and Feelings Questionnaire
SNiPA	Single nucleotide polymorphisms annotator
SNP	Single nucleotide polymorphism
SWAN	Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale
TR	Teacher report
TRF	Teacher Report Form
UK	United Kingdom
USA	United States of America
WISC	Wechsler Intelligence Scale
YLD	Years lived with disability
YSR	Youth Self-Report

Chapter 1 INTRODUCTION

1.1 THESIS OVERVIEW

In this thesis, my main aim is to investigate whether there is a causal effect of maternal smoking, alcohol and caffeine use during pregnancy on attention-deficit hyperactivity disorder (ADHD) risk in offspring. I used both observational and genetic analyses to examine this relationship using data from three longitudinal birth cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC), the Generation R (GenR) and the Norwegian Mother, Father and Child Birth Cohort (MoBa).

My thesis presents first the epidemiology and genetics of ADHD, environmental risk factors associated with ADHD, an overview of maternal prenatal substance use, and approaches used in causal inference research (Chapter 1). In Chapter 2, I present my systematic review of associations between maternal smoking, alcohol and caffeine use during pregnancy and externalising disorders: ADHD, conduct disorder (CD) and oppositional-defiant disorder (ODD) in offspring. Chapter 3 focuses on the ALSPAC, GenR and MoBa data, presenting a narrative overview, descriptive statistics and comparison of cohorts analysed. Chapter 4 presents the phenome-wide association study method in the context of my research questions, and presents results using this approach based on data from ALSPAC. Chapter 5 focuses on ADHD phenotypes in more detail, and I present results using a negative control method and polygenic risk score (PRS) analyses based on Mendelian Randomization (MR) framework. Chapter 6 explores the association between maternal prenatal alcohol exposure and ADHD in offspring by using genetic variants from alcohol metabolising genes as proxies for fetal alcohol exposure. The thesis ends with a discussion (Chapter 7) summarising findings from the different studies included, interpreting them in light of their strengths and limitations and in the context of previous evidence, and providing suggestions for future research.

1.2 EPIDEMIOLOGY OF ADHD

1.2.1 Prevalence of ADHD

ADHD is a common neurodevelopmental disorder characterised by excessive levels of hyperactivity and inattention. Although prevalence estimates vary, it has been reported that on average ADHD affects 5-8% of school aged children (up to 18 years) across different countries (Faraone et al., 2003; Polanczyk et al., 2007; Polanczyk et al., 2014). Variation in the prevalence estimates is mostly dependent on which classification system and assessment methods were used for measuring ADHD symptoms. For example, studies that have used self-reported ratings have estimated the global prevalence among 3- to 18-year-olds to be 6-7% (Polanczyk et al., 2007; Willcutt, 2012). Alternatively, studies using a multi-informant procedure have reported the global prevalence among 5-19-year olds to be 2.2% (Erskine et al., 2013). ADHD is an early onset disorder, and the highest prevalence has been reported among preschool and elementary school samples (10-11 %) (Willcutt, 2012). Although ADHD symptoms decrease with age, approximately 15% of those diagnosed in childhood show persistent symptoms of ADHD also in adulthood (Faraone et al., 2006).

1.2.2 Gender effects of ADHD

Furthermore, it has been reported that ADHD is more prevalent among boys than girls (Gaub and Carlson, 1997). A study in the UK found that boys were five times more likely to get an ADHD diagnosis than girls (O'Leary et al., 2014). Similarly, another study in the UK showed that between 2004 and 2013 the ADHD incidence rate per 10,000 person years at risk was higher among boys up to the age of 15 years and the rate becomes more equal in late adolescence (16-18 years) (Hire et al., 2018). See Figures 1.1 and 1.2.

However, it has been suggested that girls may be underdiagnosed because of the way symptoms are expressed and due to referral bias (Biederman et al., 2002). Compared with boys, girls with ADHD present more inattention symptoms which are often accompanied with internalising disorder

symptoms, and therefore ADHD diagnosis in girls may be underestimated (Biederman et al., 2005; Gershon, 2002).

Figure 1.1. ADHD incidence rates in UK per 10,000 person years at risk in the years 2004-2013. Copyright Hire et al., 2018

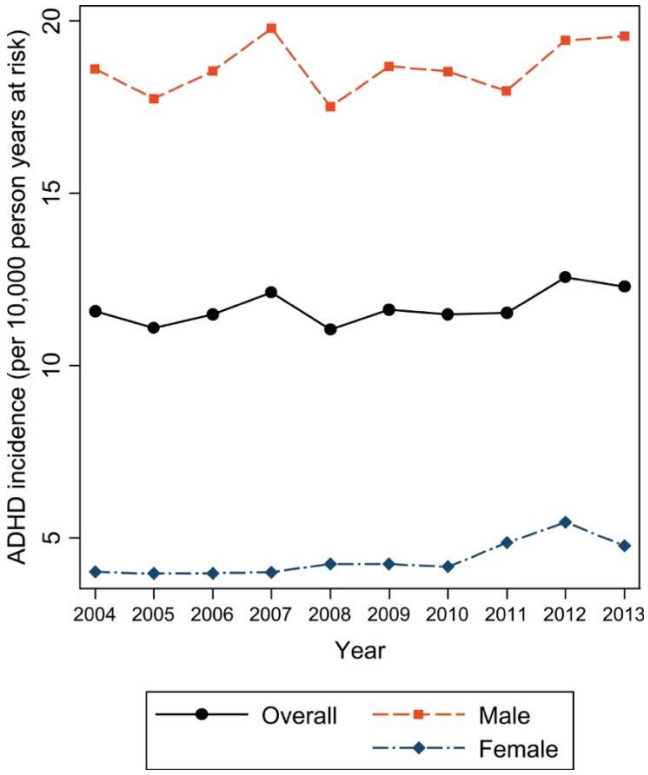
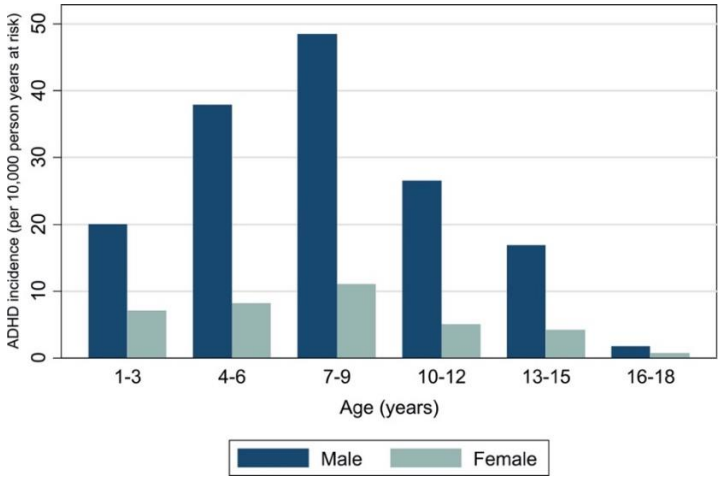


Figure 1.2. ADHD incidence rate by age of diagnosis. Copyright Hire et al., 2018



1.2.3 Symptoms and diagnostic criteria of ADHD

According to the current Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013) at least six symptoms either in the inattention or hyperactive-impulsive domains must be present for six months in two or more settings to meet the diagnosis of ADHD (Levy, 2014). A key element in diagnosing children with ADHD is to assess symptoms in different settings, usually at home and school. Very often ADHD inattention symptoms are more visible in structured settings, such as schools and therefore information from teachers is essential for ADHD assessment (Willcutt, 2012).

ADHD symptoms according to the DSM-5 (Gallo and Posner, 2016) include:

Inattention symptoms

- Fails to give close attention to details or makes careless mistakes in schoolwork, work or during other activities.
- Has difficulty sustaining attention in tasks or play activities.
- Does not seem to listen when spoken to directly.
- Does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.
- Has difficulty organising tasks and activities.
- Avoids or is reluctant to engage in tasks that require sustained mental effort.
- Often loses things necessary for tasks or activities.
- Easily distracted by extraneous stimuli or thoughts.
- Is often forgetful in daily activities.

Hyperactive-impulsive symptoms

- Fidgets with or taps hands or squirms in seat.
- Leaves seat in situations when remaining seating is expected.
- Runs about or climbs, or is restless in situations where it is inappropriate.
- Unable to play or engage in leisure activities quietly.
- Is often “on the go” acting as if “driven by a motor”.

- Talks excessively.
- Blurts out answers before questions have been completed.
- Has difficulty awaiting turn.
- Interrupts or intrudes on others.

Compared with DSM-IV, the major changes in the DSM-5 ADHD classification relate to moving the diagnosis from a disruptive behaviour disorders group to neurodevelopmental disorders, expanding the symptoms descriptions for adolescents and adults, changing the age of onset from 7 years to 12 years, and lowering the threshold from six to five symptoms in adults (Doernberg and Hollander, 2016; Gallo and Posner, 2016; Sibley and Kuriyan, 2016).

In the UK, the International Classification of Disease, 11th Revision (ICD-11) is used for diagnosing mental health disorders. Compared with the previous version (ICD-10), ADHD has been moved from the hyperkinetic disorders to the grouping of neurodevelopmental disorders, as it is classified in the DSM diagnostic system in order to make the DSM and ICD classification systems more comparable (Doernberg and Hollander, 2016; Reed et al., 2019). Both disease classification systems describe ADHD by the most dominant symptom type: inattentive, hyperactive-impulsive or combined (Reed et al., 2019).

Studies have shown that the ADHD inattentive subtype is the most prevalent subtype in children, adolescents, and adults, but not pre-school children where the hyperactive-impulsive subtype is more common (Willcutt, 2012). Further, hyperactive-impulsive symptoms have been shown to decline with age (Biederman et al., 2000) and the inattention subtype is more likely to persist into adulthood (Kessler et al., 2010). The main difficulty in diagnosing children with ADHD is that inattention and hyperactive-impulsive symptoms are also somewhat age-appropriate behaviours. It can therefore be challenging to differentiate when these symptoms go beyond what is developmentally appropriate (Faraone et al., 2006).

Several studies have also indicated that ADHD symptoms are continuously distributed, and ADHD diagnosis occurs at the extreme end of the continuum (Thapar and Lewis, 2009). It has been argued that a categorical approach, such as a clinical diagnosis, is useful when deciding whether a child should receive a medication or not. On the other hand, a dimensional approach would allow the course and severity of disorder symptoms to be tracked more closely (Rutter, 2003). For example, it has been shown that ADHD inattention symptoms exist on a severity continuum, and therefore treatment of ADHD should focus on decreasing the symptoms from a pathological level to a nonpathological level, rather than to the absence of the disorder (Lubke et al., 2009). In other words, ADHD can be defined either in a categorical or a dimensional way. In this thesis I used both a measure of diagnosis (Chapter 2) and dichotomised symptoms score (Chapter 5 and 6).

1.2.4 Comorbidities and impairment

ADHD has a high comorbidity with other psychiatric conditions (Angold et al., 1999). The most common comorbid disorders are ODD and CD (Biederman et al., 1991; Kadesjo and Gillberg, 2001), but internalising and other mental health conditions are also prevalent among children with ADHD (Gillberg et al., 2004). For example, Biederman and colleagues (1991) have shown that up to 50% of children with ADHD also meet criteria for CD or ODD. In addition, ADHD often co-occurs with autism spectrum disorders (ASD). One study showed that 13% of children diagnosed with ADHD also have accompanied ASD symptoms which is higher among young children aged 4 to 11 years (Zablotsky et al., 2020). Other studies have reported that co-occurrence of ADHD symptoms in individuals with ASD is between 30 to 50% (Leitner, 2014).

Importantly, children with ADHD are also more likely to experience difficulties at school. Several studies have indicated that children with ADHD have lower academic performance and lower grades (DuPaul et al., 2016; Loe and Feldman, 2007), and therefore children with ADHD are at higher risk for school dropout, lower qualifications and later disadvantage

in the job market (Erskine et al., 2016; Fredriksen et al., 2014). It is also widely reported that ADHD is a risk factor for later substance use (Charach et al., 2011). Several studies have shown associations between ADHD, smoking initiation, alcohol, and other substance use (Biederman et al., 2006; Osland et al., 2017).

Besides mental health impairment, deficits have been noted in children with ADHD in their cognitive and social skills, as well as in emotion regulation (Gardner and Gerdes, 2015). For instance, studies have reported that children with ADHD face more difficulties in peer relationships and very often they fail to understand the social cues needed for reciprocal interaction (Hoza, 2007; Sibley et al., 2010). Additionally, impulsive behaviour can be aversive for peers and therefore children with ADHD are often left out from groups (Hoza et al., 2005). Although ADHD is more commonly diagnosed among boys, studies on girls with ADHD have shown that girls have at least a similar degree of social difficulties as boys (Blachman and Hinshaw, 2002; Ragnarsdottir et al., 2018).

To conclude, ADHD is a complex disorder with a high comorbidity with other mental health conditions as well as impairments in various everyday life domains.

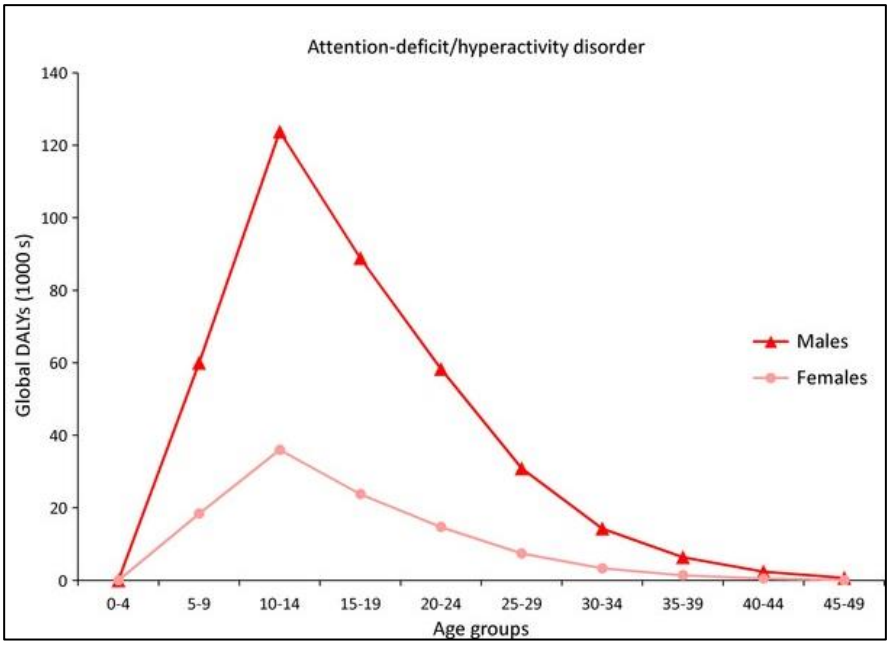
1.2.5 Societal impact

Besides the negative impact of ADHD on children's mental health and quality of life, a large body of research has described a considerable economic burden of ADHD for society as a whole. Studies have shown that ADHD has both direct and indirect costs, affecting educational attainment, risk behaviours and usage of social and health care systems (Sayal et al., 2018).

In the UK, the National Health Service (NHS) costs for ADHD were an estimated £23 million for initial assessment and £14 million annually to further specialised care in 2006 (King et al., 2006). Another study reported that in 2010 the annual costs to the NHS, social care and education services

were estimated at £670 million with the highest costs in the education system (Telford et al., 2013). Furthermore, a cohort study in the UK found that children with ADHD had a higher rate of contacts with police and criminal justice system (Ford et al., 2008). Additionally, longitudinal studies have shown that ADHD in childhood is associated with lower levels of employment and income at age 30 years (Gordon and Fabiano, 2019; Knapp et al., 2011). According to the Institute for Health Metrics & Evaluation report in 2012, the global burden of ADHD in disability-adjusted life years (DALYs) was 491,500 and ADHD was the 98th leading cause of years lived with disability (YLDs) for individuals across the age groups. The global burden was even higher for males and those with comorbid conduct disorder (Erskine et al., 2014). Figure 1.3 shows global DALYs of ADHD up to age 49 years in males and females with the highest burden in males at age 10-14.

Figure 1.3. Global years lived with disability: disability-adjusted life years (DALYs) (in 1000 s) of attention-deficit/hyperactivity disorder for males and females from ages 0 to 49 years. Copyright Erskine et al. 2014



Costs are also high with another highly comorbid neurodevelopmental disorder – ASD. It has been reported that in 2010 global prevalence of ASD was 2.4 per 1000 (Baxter et al., 2015). A study in the UK based on the Millennium Cohort and using parent-reported ADHD and ASD diagnosis

found that prevalence of ADHD among 6 to 8 years in 2008-2009 was 1.4% and in ASD 1.7% (Russell et al., 2014). Furthermore, in children age 5 to 14 years ASD was the 4th leading cause of disability out of mental health disorders and accounted 7.7 million DALYs globally in 2010 (Baxter et al., 2015). Considering that ADHD symptoms decrease within age, ASD has shown to be persistent over the life course (Baxter et al., 2015; Faraone et al., 2006) and therefore can cause higher burden than ADHD. However, given the high comorbidity between ADHD, risk taking behaviour and substance use, as well as higher risk of treatment discontinuation in adolescents and young adults (McCarthy et al., 2009; Zulauf et al., 2014), there may be substantial indirect costs of ADHD which may be difficult to estimate.

1.3 GENETIC DETERMINANTS OF ADHD

1.3.1 Heritability of ADHD

Heritability is an estimate of the proportion of variation in a trait in the population that is explained by genetic variance (Visscher et al., 2008). Heritability can be defined as broad-sense which captures the proportion of a trait variation due to the additive and non-additive genetic effects (such as interactions between alleles at the same locus or different loci (called "epistasis")), and narrow-sense which captures the proportion of a trait variation due to the additive genetic effects (Rijsdijk and Sham, 2002; Wray and Visscher, 2008).

ADHD is a highly heritable disorder with a narrow-sense heritability estimate of around 76% in both children and adults in White European populations (Faraone et al., 2005). The evidence for these estimates comes mostly from twin studies, which rely on the difference in rates of ADHD between monozygotic twin pairs who are genetically identical and dizygotic twin pairs who share 50% of their genotypes on average (Faraone and Larsson, 2019). Twin and family studies have shown that ADHD runs in families (Faraone and Doyle, 2001; Faraone and Larsson, 2019; Rietveld et al., 2003) and the genetic risk is higher for ADHD persistence into adulthood in families with first-degree relatives of probands with ADHD (Chen et al.,

2017; Franke et al., 2012). Similarly, adoption studies have shown that ADHD rates are higher among biological relatives of ADHD probands than adoptive relatives of adopted ADHD probands (Alberts-Corush et al., 1986; Sprich et al., 2000).

Evidence for strong additive genetic effects is consistent regardless of whether ADHD has been measured with maternal and/or teacher report or as a clinical diagnosis (Larsson et al., 2014; Saudino et al., 2005). Furthermore, twin studies have found that although there is a substantial genetic overlap between hyperactive-impulsive and inattention subtypes of ADHD, independent genetic effects also exist in these symptom domains (Larsson et al., 2006; McLoughlin et al., 2007). It has been reported that the narrow-sense heritability of the hyperactive-impulsive subtype is higher (about 71%) compared with the inattention subtype (about 56%) (Nikolas and Burt, 2010).

1.3.2 SNP-based heritability

Heritability can also be estimated based on single nucleotide polymorphisms (SNPs) that are captured by microarrays used in genome-wide association studies (GWASs). Recent GWAS has shown the estimate to be about 22% (Demontis et al., 2019). SNP-based heritability comes from a GWAS where the entire genome is examined in individuals to discover common genetic risk variants associated with a trait or disease of interest (Grimm et al., 2020; Yang et al., 2017). Common genetic variants occur in more than 1% of the population but normally have a small effect on a trait. Genetic variants that occur in less than 1% of the population are sometimes called rare variants (e.g., copy number variants (CNV)); these can have a bigger effect on a trait and/or to gene function compared with a common genetic variant (Bomba et al., 2017; Palladino et al., 2019).

The largest GWAS to date with 20,000 ADHD cases and 35,000 controls found 12 independent genome-wide significant ($p<5x10^{-8}$) loci associated with ADHD diagnosis which explained 5.5% of ADHD trait variation. These 12 SNPs cover 16 genes of which six are expressed in several brain regions

and have been found to be associated with educational attainment, speech problems and depression (Demontis et al., 2019).

One of the reasons why there is such a big gap in narrow-sense heritability estimates based on twin and GWAS could be that the narrow-sense heritability cannot be explained fully by common genetic variants captured by the GWAS arrays and also rare variants and other DNA variants may play a role in ADHD heritability (Manolio et al., 2009). A recent study on children with ADHD diagnosis identified some rare genetic variants (CNV) but none of these CNV overlapped with genes which were discovered in the recent GWAS of ADHD (Martin et al., 2020). Other studies have confirmed high CNV burden among individuals with ADHD, but also genetic overlap with other neurodevelopmental disorders (such as autism and Tourette syndrome) have been reported (Chawner et al., 2019; Palladino et al., 2019).

1.3.3 Polygenic risk scores

The discovery of multiple signals in GWAS have made it possible to aggregate these genetic variants into polygenic risk scores (PRSs). PRSs are calculated by summing risk alleles carried by an individual and weighting by the effect estimates detected in the GWAS. PRSs identify individuals with higher genetic liability for the disorder and could be used as a tool for genetic risk prediction (Torkamani et al., 2018). For example, it has been reported that PRSs derived from a general population sample predicted ADHD diagnosis and symptom severity in a clinical sample (Stergiakouli et al., 2015). Additionally, PRSs derived from a clinically diagnosed ADHD population predicted ADHD traits in general population (Martin et al., 2014).

Moreover, GWASs have also revealed the high polygenic nature of psychiatric disorders (Geschwind and Flint, 2015). Several studies have reported genetic correlation between ADHD and autism spectrum disorders, as well as with schizophrenia, bipolar disorder and depression (Larsson et al., 2013; Lee et al., 2013; Martin et al., 2014). Additionally,

strong genetic correlation has been found between ADHD and educational outcomes, IQ, BMI and smoking behaviour (Demontis et al., 2019). These findings highlight the complex nature of ADHD and shared genetic basis with other psychiatric disorders and behavioural traits.

In addition, studies have shown that although genetic liability for a disorder is fixed at conception, expression of genetic risk for a disorder depends on interaction with environmental exposures (Lewis and Vassos, 2020). It has been also shown that genetic nurturing, where genetic risk for a disorder could be mediated by the environment parents create for their children can affect offspring behavioural traits (Kong et al., 2018).

1.4 Environmental determinants of ADHD

As described above, there is strong evidence for genetic factors playing a role in ADHD development, and the heritability of ADHD remains stable at different developmental stages (Chang et al., 2013). However, the role of environmental factors cannot be dismissed. Twin and adoption studies have shown that approximately 10-19% of the variance within childhood externalising disorders (CD, ODD, disruptive behaviour problems) could be accounted for by shared environmental influences among siblings (Burt, 2009). However, in ADHD aetiology shared environmental factors between siblings seem to have a less substantial role, indicating that non-shared environmental factors and/or gene-environment interaction may contribute to the risk of ADHD (Burt, 2009; Faraone et al., 2015). For example, some studies have observed gene-environment interactions in children with ADHD whose mothers were smoking and consuming alcohol during pregnancy (Brookes et al., 2006; Neuman et al., 2007).

There is a large body of research also reporting that maternal pregnancy and labour complications, as well as infancy complications, such as low birth weight and prematurity are risk factors for ADHD (Halmoy et al., 2012; Sciberras et al., 2017; Silva et al., 2014). In addition, maternal postnatal risk factors (mental health, parenting behaviour), psychosocial adversity,

maltreatment and emotional trauma may affect the development of ADHD (Gonzalez et al., 2019; Mulraney et al., 2019; Russell et al., 2016).

Several studies have identified many prenatal risk factors that have been found to be associated with ADHD, such as maternal prenatal exposure to environmental toxins, and antenatal stress (Banerjee et al., 2007; Talge et al., 2007). Further, recent systematic reviews and meta-analyses indicated that maternal prenatal smoking is associated with higher risk for ADHD (He et al., 2020; Huang et al., 2018) but research of the effects of prenatal alcohol and caffeine consumption is less conclusive (Del-Ponte et al., 2016; Porter et al., 2019). As prenatal smoking, alcohol and caffeine use are the focus of this thesis, I will describe studies investigating associations between these maternal prenatal substances and ADHD in offspring more in detail in the following chapters, starting with a comprehensive systematic review in Chapter 2.

In terms of how robust the evidence base is, it is worth pointing out that it remains difficult to disentangle prenatal effects from postnatal effects (such as maternal postnatal mental health, substance use and parenting behaviour) and draw conclusions on the relative importance of each in contributing to ADHD development.

1.4.1 Harms of prenatal substance use

The Developmental Origin of Health and Disease (DOHaD) hypothesis suggests that early fetal life is a sensitive period and developmental risk factors during this time can cause negative health outcomes in later life (O'Donnell and Meaney, 2017). For example, it has been also suggested that maternal early life stress and nutrition can have a negative effect on offspring neurodevelopmental outcomes (Bale et al., 2010).

Although the majority of research on the teratogenic effects of prenatal substance use comes from animal studies, human studies have also confirmed the harmful effects of nicotine and alcohol on the developing fetus. During the first and second trimesters of pregnancy the cerebral

cortex is generated, and the majority of adult neurons are produced (Holbrook, 2016; Lambers and Clark, 1996; Rajesh, 2012). Early nicotine and alcohol exposure have been found to influence this maturation process, and can therefore cause various health risks for the fetus (Blood-Siegfried and Rende, 2010; Rajesh, 2012). The most vulnerable period to the fetus's brain development is the third trimester as during this time brain development is the most rapid and the likelihood for damage is the greatest (Richter and Richter, 2001). Adverse effects of heavier prenatal smoking and alcohol use have been well documented for a range of birth outcomes, such as low birth weight, preterm birth, miscarriage, increased infant mortality, as well as on neurobehavioral deficits in later childhood development (Forray, 2016). However, evidence is inconsistent for the effects of low to moderate prenatal alcohol consumption on child health outcomes (Mamluk et al., 2016; Mamluk et al., 2020). Research also indicates that adverse effects are dependent on the frequency, quantity and timing of substance use (Brand et al., 2019; Cluver et al., 2019; Richter and Richter, 2001).

Research on teratogenic effects of caffeine in humans is less conclusive but evidence from animal studies has shown that caffeine also affects fetal brain development (Silva et al., 2013). It has been reported that high maternal caffeine intake can have an effect on negative birth outcomes, but evidence is weaker for harmful effects of caffeine intake less than 300 mg/day (Temple et al., 2017). Given that caffeine consumption is also associated with smoking it may be difficult to disentangle specific effects of caffeine from smoking (Treur et al., 2016).

Therefore, it remains unclear whether low to moderate level prenatal substance use has a harmful effect on offspring mental health outcomes and in particular ADHD risk. Testing the DOHaD hypothesis is particularly difficult because it is not possible to use randomised control designs in pregnancy exposures (D'Onofrio et al., 2014). Furthermore, given the genetic overlap between substance use and ADHD (Wimberley et al., 2020)

it is important to address both genetic and environmental factors which may confound the association between the exposure and outcome.

1.4.2 Comorbidity of prenatal substance use

Several studies have found that prenatal smoking and alcohol use often co-occur (Lange et al., 2015; Stotts et al., 2003), and smoking behaviour (smoking initiation and smoking heaviness) is highly correlated with higher caffeine consumption (Treur et al., 2016).

Furthermore, it has been shown that using multiple substances is more common among women who are younger and with more disadvantaged social backgrounds (in terms of social class, education, and income) (Liu and Mumford, 2017; Powers et al., 2013). Pirie and colleagues (Pirie et al., 2000) found that pregnant women with low-income who used multiple substances (tobacco smoking, alcohol, and caffeine) were less likely to quit substance use compared with women who used only one substance. The same study also found that pregnant women who continued smoking were eight times more likely to drink alcohol during pregnancy and consumed more caffeine comparing with non-smokers.

Research suggests that there is a similarity between the withdrawal symptoms of caffeine and nicotine, as well as increases in fatigue and headaches among those stopping both substances simultaneously, which could be one of the reasons why some women may find it difficult to quit both of these substances at the same time (Swanson et al., 1994; Swanson et al., 1997). Furthermore, it has been reported that women who continue with substance use during pregnancy suffer more mental health problems like depression and anxiety and their perceived self-worth is lower (Massey et al., 2011). Therefore, failure to quit multiple substance use during pregnancy may be associated with environmental, physiological, and psychological factors. In addition, consumption of multiple substances during pregnancy may have a stronger effect on offspring health outcomes. One such study found that maternal prenatal exposure to alcohol, smoking

and illicit drugs accounted for the association between prenatal alcohol exposure and offspring attention problems (D'Onofrio et al., 2007).

However, because of co-occurrence of multiple substances confounding factors can differ between those individuals who use only one substance from those who use multiple substances. Therefore, it is difficult to disentangle specific effects of each substance.

1.4.3 Burden of maternal prenatal substance use

Current guidelines, both in the UK and internationally, advise pregnant women not to smoke and drink alcohol when trying to become pregnant, and to stop if pregnancy is confirmed (Department of Health, 2016; National Institute for Health and Care Excellence, 2010). The current guidelines on caffeine consumption recommend limiting daily caffeine consumption and keeping it less than 200 mg a day (Agostoni et al., 2015; Insitute of Medicine, 2014) which is equivalent to one cup of strong coffee, two cups of instant coffee or three cups of tea.

Although there is substantial evidence of negative health outcomes of prenatal substance use on the developing fetus and later childhood outcomes, prenatal substance use continues to be one of the major public health problems. The global prevalence of smoking during pregnancy was estimated to be 1.7% and with the highest rate in the European Region (Lange et al., 2018). In the UK in 2018/2019, the prevalence of smoking in the general population was 15% and among pregnant women at the time of delivery it was 11%. Although comparing with the year 2008/2009 the rate has gone down by 4%, a substantial proportion of women continue smoking during pregnancy.

The global prevalence of consuming any amount of alcohol during pregnancy in the general population was estimated to be 9-11%. However, the prevalence of alcohol use during pregnancy varies across countries and is reported to be higher in European countries compared with Middle Eastern countries (Popova et al., 2017). The same study also reported that

UK has the fourth highest estimated prevalence (41%) of prenatal alcohol use worldwide. Another study found that 79% of women in the UK drink during pregnancy and 33% at binge levels (O'Keeffe et al., 2015).

The prevalence of coffee consumption also varies worldwide (Temple et al., 2017). Nordic countries, such as Finland and Sweden have one of the highest coffee consumption levels (reported on average as 205-236 mg/day), whereas in the UK the average caffeine consumption per day is about 130 mg/day (DePaula and Farah, 2019; Fitt et al., 2013). Prenatal caffeine consumption is still an under-researched area and currently there are limited data about the prevalence of caffeine consumption during pregnancy. One cohort study in the USA reported that the majority of women stopped or decreased their caffeine consumption after pregnancy recognition (Chen et al., 2014). The same study also found that mothers who smoked were less likely to stop their caffeine consumption (from coffee, tea and soft drinks), whereas prenatal alcohol consumption did not have a similar effect.

Negative health outcomes of prenatal substance use not only impact individuals; they are also costly for the social, health and education sector. A study in the UK found that maternal smoking in pregnancy was associated with increased health-care costs during the first five years of a child's life (Vaz et al., 2018). Furthermore, according to Public Health England, in the general population alcohol was the leading risk factor for ill-health, early mortality and disability. The public health burden of alcohol is not only causing costs to health care, social and criminal justice sector but is also related to indirect costs such as lost or decreased productivity, unemployment and impact to other people (Public Health England, 2016).

In addition, prenatal alcohol consumption increases the risk of fetal alcohol spectrum disorder (FASD). FASD is an umbrella diagnosis that includes several conditions affected by prenatal alcohol exposure, such as fetal alcohol syndrome (FAS), partial FAS and alcohol-related neurodevelopmental disorder (ARND). Several studies have shown that

there is a high comorbidity and overlap in symptom presentation between FASD, ADHD and disruptive behaviours (Mattson et al., 2019; Popova et al., 2016). This further complicates differential diagnoses of FASD and ADHD, and some have questioned whether we are in the presence of co-occurring separate symptomatology (comorbidity), as opposed to different aspects of the same neurodevelopmental spectrum (Peadon and Elliott, 2010).

It has been reported that in the UK the prevalence of FASD in the general population was 61.3 cases per 10,000 and globally more than 11 million individuals up to age 18 years in the general population have FASD (Popova et al., 2017). This further indicates a high burden of prenatal alcohol exposure. However, given that FASD is largely undiagnosed in the UK health care system, actual costs related to FASD may be underestimated (Popova et al., 2012).

1.5 CAUSAL INFERENCE RESEARCH

1.5.1 Observational studies

Observational studies (e.g., cross-sectional, case-control, longitudinal cohort studies) have shown associations between maternal prenatal smoking, alcohol and caffeine use and behavioural problems in offspring (Easey, Dyer, et al., 2019; Huang et al., 2018; Mikkelsen et al., 2017). However, observational study designs and methods are subject to limitations such as the difficulty in identifying all the possible confounders (unmeasured confounding), as well as how selected confounders were assessed (measurement error leading to residual confounding), meaning that observed results may be biased (Davey Smith and Ebrahim, 2002; Gage et al., 2016). In reality it is impossible to measure all the confounders and measurement error can never be ruled out. Furthermore, several studies have measured prenatal substance use retrospectively, which may introduce recall bias (Gorber et al., 2009; Leviton, 2018). In addition, studies based on small sample sizes may yield positive association because of chance, and publication bias in the literature may appear when the majority of the published studies report positive associations (Ioannidis et al., 2014).

Another limitation in observational studies is reverse causation as in some instances it might be difficult to ascertain whether the outcome itself can have a direct effect on the exposure. However, availability of data from longitudinal birth cohorts can help to deal with the problems with reverse causation. Prospective data collection, where exposures have been measured before the outcome, can strengthen the evidence base for causality (Richmond et al., 2014). Still, the limitations with unmeasured confounding remain. Additionally, selection bias in how the study participants were selected, as well as differences in data collection and loss to follow-up can bias exposure-outcome associations (Munafò et al., 2018).

Therefore, considering these limitations, observational studies cannot fully confirm causality but combined with multiple methods as part of a triangulation approach (see paragraph 1.5.4 “Triangulation in Causal Inference”), can provide more support as to whether a causal effect exists. It has been emphasised that data integration using multiple approaches is the key criterion for causal inference research (Fedak et al., 2015).

1.5.2 Quasi-experimental designs

Quasi-experimental designs (such as twin designs, negative control, and sibling comparison) have been suggested as useful approaches to establish stronger causal inference. This is because these studies strive to compare ‘like with like’ groups of individuals by, at least to some extent, accounting for both environmental and genetic confounding (D'Onofrio et al., 2020). I will discuss these designs more in detail in Chapter 5. Studies based on negative control and sibling comparison designs have provided stronger evidence that the association between maternal smoking during pregnancy and ADHD in offspring is likely not to be causal and may instead be explained by confounding (Gustavson et al., 2017; Skoglund et al., 2014). Currently there are fewer quasi-experimental studies investigating the effects of prenatal alcohol exposure on ADHD in offspring and one such study did not find strong evidence for a causal effect, whereas the other study suggested a weak effect (D'Onofrio et al., 2007; Eilertsen et al., 2017). To my knowledge, none of the studies using quasi-experimental designs

have examined the effects of prenatal caffeine exposure on ADHD in offspring.

1.5.3 Mendelian Randomization (MR)

As an alternative to the conventional observational study designs, and another example of a quasi-experimental design, is the use of proxy genetic variants. For example, genetic variants which have been found to be associated with an exposure of interest in a GWAS can be used as a non-confounded proxy or predictor for measuring exposure-outcome associations (Richmond et al., 2014). Mendelian Randomization (MR) is one such method that uses genetic variants associated with the modifiable risk factor as a proxy for that exposure to test for a causal effect on the outcome (Davey Smith and Ebrahim, 2004). However, three main assumptions need to be met before conducting MR (Davies et al., 2018): 1) the relevance assumption states that genetic variants are associated with the exposure of interest; 2) the independence assumption states that there is no common cause with the outcome (e.g., no confounding); and 3) the exclusion restriction assumption states that genetic variants do not affect the outcome directly other than via the exposure.

The advantages of MR compared with the observational study designs are that genetic variants should not be affected by confounders or reverse causation, are much less affected by measurement error and very rarely does reverse causation come into play (Davey Smith and Ebrahim, 2004).

Although MR has become a popular method in many settings investigating population health and disease aetiology, including when investigating intrauterine exposures, some limitations should be acknowledged, mainly in the form of biases occurring whenever the three core assumptions are not satisfied. First, MR studies may suffer from low statistical power as genetic variants explain a small proportion of the variance in a trait. Second, disease risks may differ in different ethnic populations and therefore may induce confounding due to genetic ancestry. Third, pleiotropy may be operating, whereby the same genetic variant is affecting the outcome

directly and not via the exposure (Davey Smith and Ebrahim, 2004; Richmond et al., 2014).

1.5.4 Triangulation in causal inference research

It is widely acknowledged that there is no single method that can enable us to draw strong conclusions on causality as each method has their own limitations and different source of biases (Lawlor et al., 2016). However, combining different methods can help to gain stronger support for a causal effect. For example, if different methods are pointing towards results in the same direction then stronger conclusions can be made. This is because it is unlikely that different methods are biased in the same way. On the contrary, if the results differ between different methods used in the study, further investigations should be made.

The concept of "triangulation" refers to the integration of different approaches within the single or in multiple studies addressing the same research question (Lawlor et al., 2016). This is particularly relevant when investigating the DOHaD hypothesis. Considering that both environmental and genetic confounding can affect the associations between prenatal exposures and child outcomes, it is important to address alternative hypotheses and apply multiple methods before drawing conclusions on causality (D'Onofrio et al., 2014).

1.6 CHAPTER SUMMARY

To summarise, even though ADHD is a well-researched topic, there is still inconsistency in findings regarding whether the association between maternal prenatal smoking, alcohol and caffeine use and ADHD risk in offspring is causal. Quasi-experimental studies have shown that the association between maternal prenatal smoking and ADHD is likely to be confounded, but many of these studies have not examined ADHD subtypes separately. In addition, findings are less conclusive on the effects of prenatal alcohol and caffeine exposure on ADHD in offspring. Given the high public health burden of ADHD, it is crucial to understand causal pathways of ADHD development in children. If maternal smoking, alcohol,

and caffeine consumption during pregnancy are causally associated with ADHD symptoms in offspring, these harmful behaviours could be potential targets for public health interventions. Moreover, this knowledge can help to target children at risk for ADHD and provide interventions at earlier stages, in order to reduce or prevent negative outcomes.

1.7 THESIS FOCUS

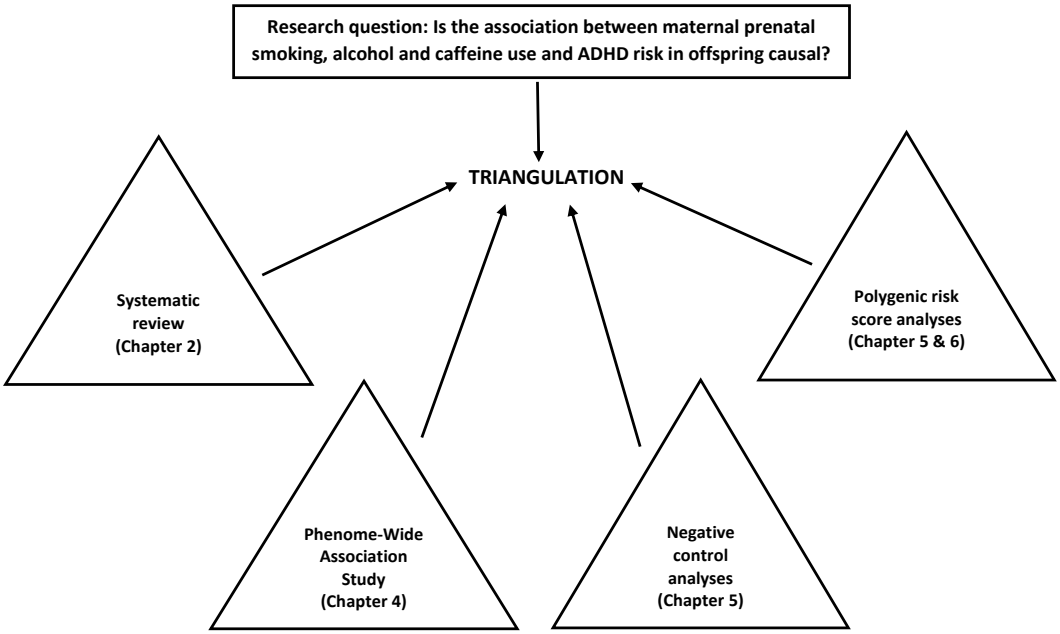
1.7.1 Aims

The aim of this thesis is to investigate the causal effects of maternal smoking, alcohol and caffeine use during pregnancy on risk of ADHD total symptoms, as well as separately for hyperactive-impulsive and inattention symptom domains in offspring. Triangulating evidence by using systematic review method (Chapter 2), observational (Chapter 5) and genetic analyses (Chapter 4, 5 and 6) and replicating findings in different cohorts, is the essence of this work.

1.7.2 Methods

In this thesis, I use different research methods. A systematic review is used to find evidence whether a current research support a causal role of prenatal smoking, alcohol and caffeine exposures on offspring externalising disorders (Chapter 2). A targeted Phenome-Wide Association Study is used to observe potential causal and pleiotropic effects of maternal prenatal smoking and caffeine consumption on various mental health outcomes in offspring (Chapter 4). Negative control and polygenic risk score analyses are used to investigate whether there is a causal effect of maternal prenatal smoking, alcohol and caffeine use on ADHD risk in offspring (Chapters 5 and 6). A visual overview of the methodological approach used in this thesis is given in Figure 1.4. More details about each method are given in the chapters where these methods were used.

Figure 1.4. Visual overview of the methodological approach



Chapter 2 PRENATAL SMOKING, ALCOHOL AND CAFFEINE EXPOSURE AND OFFSPRING EXTERNALISING DISORDERS: A SYSTEMATIC REVIEW

In Chapter 1, I gave an overview of the background and complexities of ADHD, as well as described prevalence and harms of prenatal substance use. Furthermore, as described in Chapter 1, there is more evidence that the association between maternal prenatal smoking and ADHD is likely to be confounded, but evidence is inconsistent for the associations with alcohol and caffeine exposure.

For this chapter I conducted a systematic review to examine current research and evaluate whether existing research has found evidence for a causal relationship between maternal prenatal smoking, alcohol and caffeine consumption and externalising disorders in offspring. I further appraised published studies in terms of methods used and provided suggestions for future studies to improve causal interpretation.

2.1 INTRODUCTION

Several studies have indicated that maternal health behaviours during pregnancy, such as smoking, alcohol, and caffeine consumption, may contribute to offspring externalising problems (Keyes et al., 2014; Mikkelsen et al., 2017; Pagnin et al., 2019) (problems such as attention-deficit hyperactivity disorder (ADHD), conduct disorder (CD) and oppositional-defiant disorder (ODD)). However, it remains unclear whether these reflect true causal effects or rather the associations are due to residual confounding in particular due to socioeconomic factors such as socioeconomic position, education, income and maternal age (Berglundh et al., 2020; Kelly et al., 2012; Loomans et al., 2012; Palmer et al., 2016; Robinson et al., 2010; Russell, Ford, et al., 2015). As discussed in Chapter 1, this is of considerable public health importance, since smoking, alcohol and caffeine consumption are all common exposures and although current guidelines in UK recommend abstaining from smoking and alcohol

consumption (Department of Health, 2016; National Institute for Health and Care Excellence, 2010) and limiting daily caffeine consumption to 200mg during pregnancy (Agostoni et al., 2015), most women still use these substances at some point in pregnancy (Lange et al., 2018; O'Keeffe et al., 2015).

A recent systematic review (Easey, Dyer, et al., 2019) found evidence of an association between low to moderate level maternal alcohol use during pregnancy and offspring behavioural and conduct problems. Similarly, other systematic reviews and meta-analyses have reported an association between maternal smoking during pregnancy and offspring CD and ADHD (He et al., 2020; Huang et al., 2018; Ruisch et al., 2018). However, these reviews are based on conventional observational studies which do not provide strong evidence of causality, given well described limitations such as unmeasured and residual confounding. In fact, the only review to date to triangulate evidence from different study designs many of which robust to confounding, concluded that there was no robust evidence for an effect of maternal alcohol use during pregnancy on behavioural phenotypes including ADHD (Mamluk et al., 2020).

As well as socioeconomic confounding, the observed associations could also be explained by shared genetic influences (i.e., genetic confounding). Several studies have reported shared genetic liability between ADHD, CD and substance use (Grant et al., 2015; Treur et al., 2021; Vilar-Ribo et al., 2020) and in particular, maternal genetic risk for ADHD has been found to be associated with smoking during pregnancy (Leppert et al., 2019). Therefore, it is possible that the association between prenatal substance exposure and externalising disorders in offspring could be explained by genetic transmission from mothers to offspring. Furthermore, these recent reviews have also highlighted the need for further investigation into whether there is a causal effect of maternal substance use during pregnancy on externalising problems in offspring and use genetically informative study designs to disentangle potential causal effects.

I conducted an updated systematic review to synthesise and evaluate the evidence for a causal relationship between maternal smoking, alcohol and caffeine consumption during pregnancy and diagnosis of ADHD, CD and ODD in offspring to reduce the potential heterogeneity in outcome assessment with self-reported measures. My main focus was on establishing whether the literature supports a causal role for these exposures; therefore I chose to build on existing research but not limiting to any study designs and specifically including studies that account for genetic effects, in addition to conventional observational approaches. Although in the DSM-5 ADHD is classified as a neurodevelopmental disorder, there is a high comorbidity between ADHD, CD and ODD (Singh, 2008) and prenatal substance use may have somewhat different effect on these outcomes. Therefore, I was interested whether associations differed across these externalising disorders.

2.2 METHODS

I published the protocol for this systematic review on the Open Science Framework (10.17605/OSF.IO/D9WZK) and PROSPERO (ID: CRD42018094810). I followed PRISMA and MOOSE guidelines, as well as Cochrane methods, where applicable.

2.2.1 Search strategy

I performed electronic searches using Web of Science, Embase, PsycINFO and Medline databases from the Ovid platform. In addition, I checked the reference lists of all previous reviews that were identified. My search strategy included following search terms:

1. Outcome terms: "attention deficit disorder" OR "hyperactiv*" OR "impulsiv*" OR "ADHD" OR "attention deficit hyperactivity" OR “ADD” OR "externali?ing" OR “conduct disorder” OR “behavio* disorders” OR “behavio* problem*” OR “disruptive behavio*” OR “oppositional defiant disorder”.

2. Exposure terms: "alcohol*" OR "tobacco" OR "caffein*" OR "drink*" OR "ethanol" OR “drinking” OR "smoking" OR "cigarette*" OR "nicotine" OR "coffee" OR "tea" OR "energy drink*"OR “taurine”
3. Population terms: “pregnan*” OR “perinatal” OR “prenatal” OR “intrauterine*” OR “utero” OR” f?etal” OR “gestation” OR “trimester”

I included relevant MeSH terms when searching from the Ovid platform. An example search is shown in Appendix 2.1. The search was performed including studies up to 26th of April 2018.

2.2.2 Inclusion and exclusion criteria

Inclusion criteria were: 1) publication in a peer reviewed journal in English language, 2) observational studies (including cross-sectional, case-control, longitudinal, and cohort studies which also included negative control studies), 3) maternal smoking, alcohol and caffeine use measured during pregnancy, and 4) diagnosis of ADHD, CD and ODD in offspring.

Exclusion criteria for the study were: 1) animal studies, 2) reviews, 3) conference and/or meeting abstracts, 4) studies with no comparison group, 5) fetal alcohol spectrum disorder (FASD) studies, as several studies have shown an association between heavier drinking and FASD; and 6) studies with comorbid autism spectrum and tic disorders due to the somewhat different aetiology of coexistence of these disorders.

2.2.3 Study selection and data extraction

I carried out selection of studies in three stages: stage 1 included screening titles and abstracts, stage 2 included full text screening, and stage 3 included data extraction and risk of bias assessment. Study selection and data extraction took place by three reviewers: I conducted 100% of study screening, data extraction and risk of bias assessment; 75% check was conducted by PhD student Kirsten Westmoreland, and 25% check by PhD student Laura Schellhas. Any disagreements were resolved by consensus.

If included studies measured multiple exposures and outcomes, I extracted data separately for each exposure and outcome. Additionally, if more than one follow-up period was reported, I extracted data from the latest follow-up period as per Cochrane guidance (Higgins et al., 2020).

2.2.4 Risk of bias assessment

I assessed risk of bias using the Newcastle Ottawa Scale (NOS) for cohorts and case-control studies (Wells et al., 2013). I evaluated included studies based on three categories: 1) Selection, 2) Comparability, and 3) Outcome. I ranked studies as low, medium or high risk of bias based on a rating system (maximum of 9 points, see Appendix 2.2). I conducted a risk of bias assessment and a check of 100% was carried out by other PhD students. Points given to each study are shown in Appendices 2.3 and 2.4.

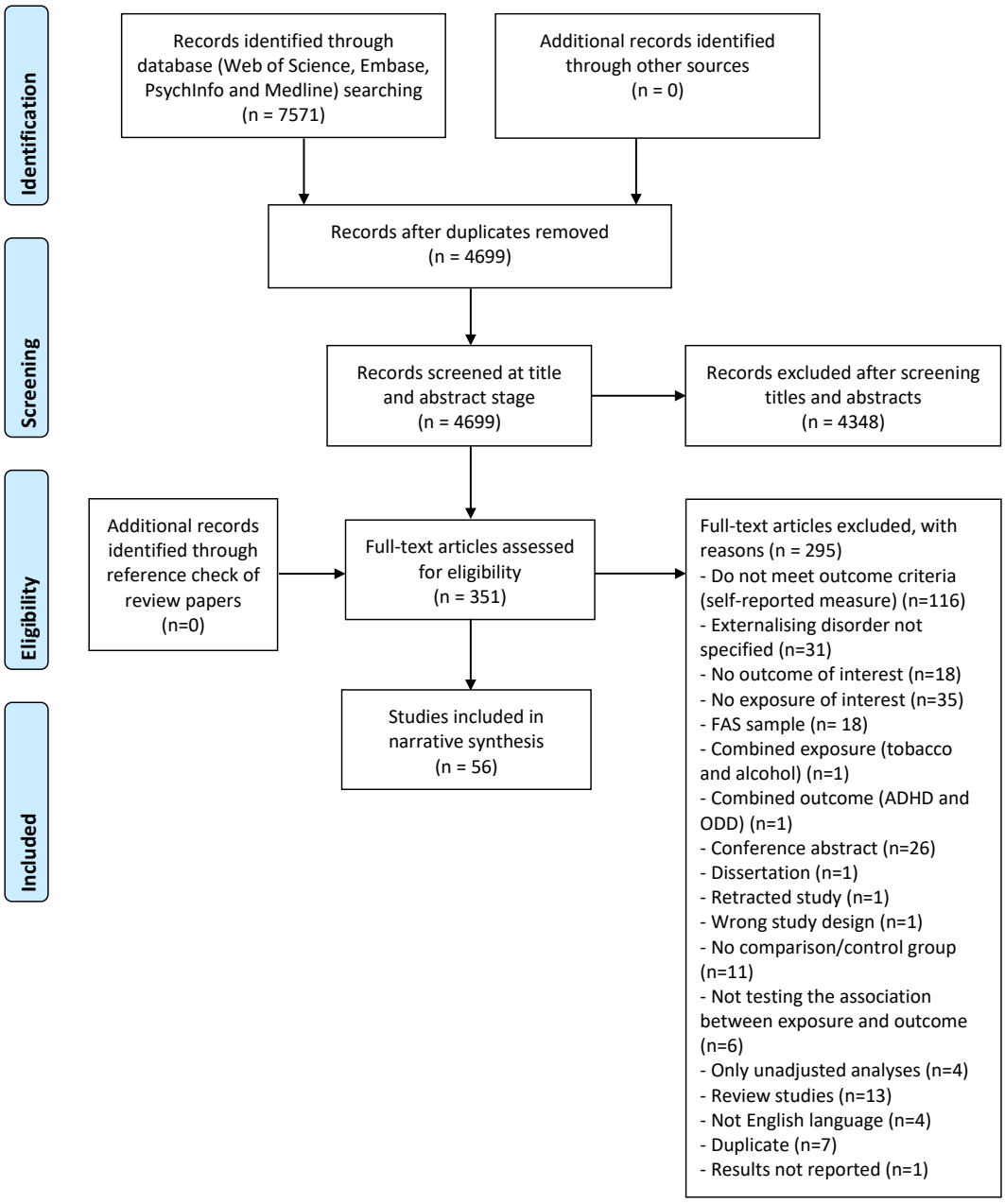
2.3 RESULTS

2.3.1 Results of literature search

In total 4,699 articles were identified (after removing duplicates) of which 351 were included in the full text screening. Of these, 295 were excluded mainly because of non-specific outcome measure (n=31), wrong exposure (n=35) or not meeting outcome criteria (i.e., single reporter measure) (n=116). The list of studies excluded, including a reason is shown in Appendix 2.5. One study could not be used as the results were not reported and the remaining 56 articles were included in the current review (see Figure 2.1).

I further contacted study authors if relevant details were missing. The list of studies which could not be included due to missing data are listed in Appendix 2.6. No further articles were identified from the reference check of review papers.

Figure 2.1. PRISMA Flowchart of search strategy



When I registered the study protocol, I planned to conduct a meta-analysis. However, considering differences in study designs, methods, exposure assessments and age at outcome assessment, a meta-analysis was not conducted. I therefore conducted a narrative synthesis of the current research and emphasized limitations in existing studies and provided suggestions for future research.

2.3.2 Characteristics of included studies

Characteristics of included studies are shown in Appendices 2.7 and 2.8. Of the included studies, 26 were North American, 20 European of which 12 were Scandinavian, 4 Australian, 4 South American and 2 Asian. Of the included studies, 50 measured smoking exposure, 13 measured alcohol exposure and 4 studies measured caffeine exposure.

Of the included 28 cohort and longitudinal studies and 6 cross-sectional studies, 5 studies were based on selective populations, such as participants from indigenous culture, areas of lower socioeconomic status, as well as participants of depressed probands. Additionally, three studies were conducted in twins. Of the 22 case-control studies included, 6 studies selected cases and controls from clinical and/or hospital-based sample and 2 studies were conducted in twins.

Follow-up time ranged from 2 to 37 years in cohort and longitudinal studies. Out of the 56 included studies, eight studies reported results separately for boys and girls (N=147 to 968,665), two studies were conducted only in boys (N=177 to 400) and two studies only in girls (N=228 to 1,936).

2.3.3 Assessment of exposures

2.3.3.1 Smoking

Of the 50 studies on smoking exposure, 22 studies (44%) used cohort and/or longitudinal design, 6 studies (12%) used cross-sectional, and 22 studies (44%) used case-control study design (see Appendices 2.7 and 2.8). Sample sizes ranged from 147 to 968,665 participants. A total of eight (36%)

of the included cohort studies used a binary exposure measure of which three studies used a cut-off <10 cigarettes per day. Of the cross-sectional studies, four studies used also a binary exposure measure. 16 (57%) studies used different categorical measures of which one study included occasional smokers to the group of no smokers.

A total of 11 (50%) of the included cohort and longitudinal studies assessed smoking during pregnancy prospectively. Three of these studies measured smoking in each pregnancy trimester, three studies in two pregnancy trimesters and the remaining three studies measured smoking at one time point during pregnancy. 12 (56%) studies assessed smoking some years after child's birth. Four cross-sectional studies assessed smoking retrospectively and two studies did not provide these details.

Of the 22 included case-control studies, 4 studies (18%) assessed smoking prospectively and 18 (82%) studies retrospectively. Three studies (14%) assessed smoking in each pregnancy trimester, one study during the second pregnancy trimester and 18 (82%) studies did not provide details of the pregnancy trimester during which smoking was assessed.

2.3.3.2 Alcohol

Of the 13 studies on alcohol exposure, 7 (50%) were cohort and longitudinal studies, 2 (17%) used cross-sectional design and 4 (33%) were case-control studies (see Appendices 2.7 and 2.8). Total sample size ranged from 546 to 34,283 participants.

Of the 9 included cohort, longitudinal and cross-sectional studies, 6 studies (67%) used different categorical measures and 2 studies (22%) used a binary measure. One longitudinal cohort study measured alcohol exposure using the continuous score from the AUDIT scale. Of the 4 case-control studies included, 3 studies used a binary measure, and one study used a categorical measure.

Out of these 13 studies, 3 studies (23%) assessed alcohol consumption prospectively, 9 studies (69%) retrospectively and one study did not provide

these details. One study assessed alcohol consumption in each pregnancy trimester, one study during the 1st pregnancy trimester and other two during the 1st and 3rd pregnancy trimester or 1st trimester and beyond.

2.3.3.3 Caffeine

Of the 4 studies on caffeine exposure, 2 used a cohort study design, one study was cross-sectional and the other used a case-control design. The total sample size ranged from 2,419 to 24,068 participants (see Appendices 2.7 and 2.8).

Two studies used categorical measures of caffeine exposure, of which one study included 'some' caffeine consumption as a baseline. Two other studies used a binary measure of which one used none to less than one cup per day as a reference. Two studies derived daily caffeine consumption from coffee and tea/mate intake, one study only from coffee and one study did not specify the source of caffeine in their analyses. Two studies assessed caffeine consumption prospectively of which one during the 2nd pregnancy trimester. The other two studies measured caffeine consumption retrospectively, of which one study asked about caffeine consumption in each pregnancy trimester and the other study did not specify in which pregnancy trimester caffeine intake was assessed.

2.3.4 Assessment of outcomes

2.3.4.1 ADHD

Of the 56 included studies, 47 studies measured ADHD. Of these studies, two focused only on ADHD inattentive subtype and three ADHD combined or hyperactive-impulsive and inattentive subtypes.

Fourteen studies (30%) used hospital or national registry databases for ADHD diagnosis and/or ADHD medication use. 23 studies (49%) used diagnostic interviews and most commonly the Diagnostic Interview Schedule for Children (DISC) and the Schedule for Affective Disorders and Schizophrenia (K-SADS) were used. Additionally, the Missouri Assessment of Genetics Interview for Children (MAGIC) and the Preschool Age

Psychiatric Assessment (PAPA) were also used. Furthermore, two studies used the Development And Well-Being Assessment (DAWBA) maternal and teacher reports for generating ADHD diagnosis called "DAWBA bands", five studies (11%) derived ADHD diagnosis based on clinical assessment or by using multiple evaluations by mothers, teachers and clinicians. Three studies (6%) used parent report of whether their child had been diagnosed with ADHD.

Offspring age at assessment varied from 4 to 37 years. 5 studies were assessed at offspring age below 6 years, 32 studies were assessed at offspring age between 6 to 13 years, 5 studies at offspring age 14 to 18 years, 4 studies were assessed in adulthood (at age 20 to 37 years) and one study did not provide these details.

2.3.4.2 CD and ODD

Of the 56 studies, 12 studies measured conduct disorder and 6 studies measured ODD. All studies derived diagnosis using diagnostic interviews (either DISC, K-SADS or PAPA) and the World Health Organization's Composite International Diagnostic Interview (CIDI).

Offspring age at CD assessment varied from 6 to 21 years. Four studies were assessed at offspring age from 8 to 15 years, six studies from 6 to 17 years, one study was assessed in adulthood and one other study did not provide these details. Offspring age at ODD assessment varied from 4 to 21 years. Two studies assessed ODD when offspring were aged 4 years, three studies at offspring age 11 to 17 years, and one study in adulthood (21 years).

2.3.5 Inclusion of confounding variables

The majority of studies adjusted for socio-economic variables (social class, education, income, marital status), as well as for maternal age, offspring age and gender. Only a few studies adjusted for maternal mental health during pregnancy and none of the studies considered partner's substance use as a potential confounder in their analyses. The list of confounders

included in the multivariable analyses are shown in Appendices 2.9 and 2.10.

2.3.6 Summary of findings

An overview of results as reported in the studies is shown in Appendices 2.7 and 2.8.

2.3.6.1 Association between smoking during pregnancy and ADHD in offspring

Out of the 56 studies, 43 assessed the association between maternal smoking during pregnancy and ADHD in offspring, of which 18 (42%) were cohort and longitudinal studies, 4 (9%) cross-sectional and 21 (52%) case-control studies.

Of the included cohort and longitudinal studies 12 (69%) found a positive association between maternal smoking during pregnancy and ADHD in offspring, whereas 6 studies (26%) did not observe evidence for any association (N=147 to 2,243) (Ball et al., 2010; Fergusson et al., 1998; Nigg and Breslau, 2007; Sagiv et al., 2013; Weissman et al., 1999). However, three of these studies that did not report a positive association used a sample measured when offspring were in late adolescence (16-18 years) or adulthood (37 years) (Ball et al., 2010; Fergusson et al., 1998; Weissman et al., 1999).

Seven studies which found a positive association used samples from prospective longitudinal cohorts and large registries (N=5,758 to 986,046) (Gustavson et al., 2017; Langley et al., 2012; Lindblad and Hjern, 2010; Obel et al., 2011; Obel et al., 2016; Skoglund et al., 2014; Zhu et al., 2014). These studies enabled the authors to take into account environmental and/or genetic confounding by using quasi-experimental designs, such as parental and sibling comparison designs. Six of these studies concluded that the association is most likely explained by confounding (Gustavson et al., 2017; Langley et al., 2012; Lindblad and Hjern, 2010; Obel et al., 2011; Obel et al., 2016; Skoglund et al., 2014). Two studies claimed that the association was stronger with maternal smoking compared to paternal smoking indicating a potential causal intrauterine effect (Nomura et al., 2010; Zhu et al., 2014). One of these studies was conducted in

the Danish National Birth Cohort (N=86,812) and other was a longitudinal study in USA (N=209).
Moreover, six studies that observed a positive association adjusted for birth weight or other perinatal factors that could be potential mediators or lead to spurious association because of collider bias (Braun et al., 2006; Froehlich et al., 2009; Koshy et al., 2011; Pohlabeln et al., 2017; Schmitt and Romanos, 2012; Sciberras et al., 2011). In addition, two twin studies concluded that prenatal smoking was a common risk factor among MZ (monozygotic) twins concordant for ADHD (Knopik et al., 2005; Lehn et al., 2007).

All four included cross-sectional studies and of the included case-control studies, 18 studies (86%) found a positive association between maternal smoking during pregnancy and ADHD in offspring, whereas three studies (14%) did not (Ketzer et al., 2012; Wiggs et al., 2016; Yoshimasu et al., 2009) and two of these studies were conducted in small samples (N=372 to 450) (Ketzer et al., 2012; Yoshimasu et al., 2009). Eight of these studies that observed a positive association adjusted for parental ADHD to account for potential genetic liability, but the association remained (Altink et al., 2009; Arnold et al., 2005; Biederman et al., 2009; Gard et al., 2016; Mick et al., 2002; Milberger et al., 1996; Milberger et al., 1998; Schmitz et al., 2006). However, another case-control study found that maternal smoking during pregnancy was shared between affected and unaffected siblings indicating that prenatal smoking is a weak risk factor for ADHD (Oerlemans et al., 2016).

Six studies examined the association with ADHD subtypes (Gard et al., 2016; Ketzer et al., 2012; Neuman et al., 2007; Schmitz et al., 2006; Todd and Neuman, 2007; Wiggs et al., 2016). One of these studies was conducted in girls only and observed an association with hyperactive-impulsive symptoms but not with inattention symptoms (Gard et al., 2016). In contrast, one study observed an indirect effect of prenatal smoking on inattention symptoms via memory span deficits (Wiggs et al., 2016). Two other studies focused only on the inattention subtype and were based on the same sample (Ketzer et al., 2012; Schmitz et al., 2006), however only one study found an association (Schmitz et al., 2006). Two of the remaining studies investigated gene-environment interactions in the

same sample of twins and found a positive effect between maternal smoking during pregnancy and child genotype in children with the combined ADHD subtype (Neuman et al., 2007; Todd and Neuman, 2007). However, two other studies that also investigated gene-environment interaction – but focused on overall ADHD and used a sample of singletons – did not find an interaction effect (Altink et al., 2008; Altink et al., 2009).

Of the six studies which investigated gender differences (Braun et al., 2006; Obel et al., 2011; Obel et al., 2016; Silva et al., 2014; Talati et al., 2017; Weissman et al., 1999), one study found a stronger association between maternal smoking during pregnancy and ADHD in girls (Braun et al., 2006) and another study in boys (Talati et al., 2017), but there was no evidence of a gender difference in the remaining four studies. Furthermore, of all the included studies on smoking exposure, 14 studies (33%) also examined dose-response relationship of which 11 studies observed a dose-dependent association (Gustafsson and Kallen, 2011; Knopik et al., 2006; Koshy et al., 2011; Lindblad and Hjern, 2010; Obel et al., 2011; Obel et al., 2016; Pineda et al., 2007; Pohlabeln et al., 2017; Schmitz et al., 2006; Sciberras et al., 2011; Skoglund et al., 2014).

2.3.6.1.1 Strength of evidence based on NOS score

In total eight longitudinal and cohort studies were rated as low risk of bias (7-9 points). Six of these studies were based on quasi-experimental designs (Gustavson et al., 2017; Lindblad and Hjern, 2010; Obel et al., 2011; Obel et al., 2016; Skoglund et al., 2014; Zhu et al., 2014), one study used a twin sample (Lehn et al., 2007) and another study was based on a prospective cohort (Sagiv et al., 2013). Seven studies concluded that the association between maternal smoking during pregnancy and ADHD in offspring is unlikely to be a causal. This was in contrast with two studies rated as very high risk of bias (0-3 points) (Koshy et al., 2011; Nomura et al., 2010) and three other studies rated as high risk of bias (4-5 points) (all cross-sectional designs) (Braun et al., 2006; Froehlich et al., 2009; Schmitt and Romanos, 2012) which found a positive association.

In total eight case-control studies were rated as low risk of bias and seven of these studies found a positive association (Altink et al., 2009; Arnold et al., 2005; Gustafsson and Kallen, 2011; Joelsson et al., 2016; Linnet et al., 2005; Schmitz et al., 2006; Silva et al., 2014; Yoshimasu et al., 2009), but these studies do not account for genetic effects and some of these are prone to recall bias, therefore conclusions about causality should be interpreted with caution.

2.3.6.2 Association between smoking during pregnancy and CD and ODD in offspring

Out of the 56 included studies, 10 investigated the association between maternal smoking during pregnancy and CD in offspring of which 5 were cohort and longitudinal studies, 2 cross-sectional studies and 3 case-control studies. Six studies (60%) found an association between maternal smoking during pregnancy and CD in offspring (Biederman et al., 2017; Biederman et al., 2009; Braun et al., 2008; Nigg and Breslau, 2007; Talati et al., 2016; Wakschlag et al., 1997). However, four of these studies used a clinical or hospital referred sample (Biederman et al., 2017; Biederman et al., 2009; Talati et al., 2016; Weissman et al., 1999). One study observed an interaction effect between maternal prenatal smoking and child genotype (Talati et al., 2016). In the three studies that did not find evidence of an association, two studies used a sample of offspring in late adolescence (16-18 years) (Fergusson et al., 1998; Weissman et al., 1999) and one study found an indirect effect via neuropsychological functioning (Wiggs et al., 2016).

Out of the 56 studies, six studies (11%) investigated the association between maternal smoking during pregnancy and ODD in offspring of which three were cohort and longitudinal studies, one cross-sectional study and two were case-control studies. Two studies (N=798 to 995) found an association with maternal smoking during pregnancy (Ellis et al., 2012; Nigg and Breslau, 2007) and four studies did not (N=215 to 5,924) (Biederman et al., 2017; Nomura et al., 2010; Russell, Johnson, et al., 2015; Wiggs et al., 2016). Among the studies that did not observe the association, one study found an indirect effect via neuropsychological

functioning similarly to the effect observed for ADHD and CD (Wiggs et al., 2016). Two studies measured ODD in adolescence (15 years) and adulthood (21 years) where disorder manifestation could differ from childhood (Biederman et al., 2017; Russell, Johnson, et al., 2015). One other study was conducted in a small sample (N=215) and may be influenced by low power to detect an effect (Nomura et al., 2010).

2.3.6.2.1 Strength of evidence based on NOS score

Only one study based on smoking and CD was rated as low risk of bias (8 points) and this study did not find evidence for an association between prenatal smoking and CD (Fergusson et al., 1998). Two studies rated as very high risk of bias (2-3 points) did not find an association between prenatal smoking and ODD (Nomura et al., 2010; Russell, Johnson, et al., 2015). Other studies rated as high risk of bias (4-6 points) found an association between prenatal smoking and CD and ODD in offspring (Biederman et al., 2009; Braun et al., 2008; Ellis et al., 2012; Nigg and Breslau, 2007; Talati et al., 2016; Talati et al., 2017; Wakschlag et al., 1997; Weissman et al., 1999), but two studies were based on cross-sectional or case-control design which cannot prove causality (Biederman et al., 2009; Braun et al., 2008) and other four studies used a clinical or hospital referred sample (Talati et al., 2016; Talati et al., 2017; Wakschlag et al., 1997; Weissman et al., 1999).

2.3.6.3 Association between alcohol consumption during pregnancy and ADHD in offspring

Out of the 56 studies, 9 investigated the association between maternal prenatal alcohol consumption and ADHD in offspring of which 4 were cohort and cross-sectional studies (N=679 to 34,503), 1 was longitudinal twin study (N=1,936) and 4 were case-control studies (N=372 to 2,419). The longitudinal twin study found a positive association only with heavier alcohol use (Knopik et al., 2005).Three (33%) case-control studies found a positive association with maternal alcohol consumption during pregnancy (Kim et al., 2009; Mick et al., 2002; Pineda et al., 2007) of which one used heavier drinking (drunkenness during the first 2 months) as the exposure (Pineda et al., 2007). Of the two other studies, one was

conducted in a hospital referred sample (Mick et al., 2002) and the other failed to adjust for many relevant confounders (Kim et al., 2009).

2.3.6.3.1 Strength of evidence based on NOS score

Only one study based on alcohol exposure and ADHD was rated as low risk of bias (9 points) and this study did not find evidence for an association between prenatal alcohol exposure and ADHD (Sagiv et al., 2013). Two other longitudinal cohort studies rated as high risk of bias (5-6 points) also did not find evidence for an association (Eilertsen et al., 2017; Pohlabeln et al., 2017). Out of four case-control studies rated as high risk of bias (5-6 points), three studies reported an association between prenatal alcohol exposure and ADHD in offspring (Kim et al., 2009; Mick et al., 2002; Pineda et al., 2007) and one study did not (Ketzer et al., 2012).

2.3.6.4 Association between alcohol consumption during pregnancy and CD and ODD in offspring

Out of the 56 studies, 4 cohort and cross-sectional studies investigated the association between maternal alcohol consumption and CD and ODD in offspring (N=546 to 5,924). Three studies were on CD (Fergusson et al., 1998; Larkby et al., 2011; Whitbeck and Crawford, 2009) and one in ODD (Russell, Johnson, et al., 2015). No association was observed with ODD, but two studies found an association between maternal alcohol consumption during pregnancy and CD in offspring (Larkby et al., 2011; Whitbeck and Crawford, 2009). However, both of these studies found the association with heavier alcohol consumption and binge drinking, and one study used a sample based on indigenous culture (Whitbeck and Crawford, 2009). The study that did not observe an association with CD was a prospective longitudinal cohort in New Zealand and CD was assessed when offspring were aged 16-18 years (Fergusson et al., 1998).

2.3.6.4.1 Strength of evidence based on NOS score

Two studies based on alcohol exposure and CD were rated as low risk of bias (8 points). One of these studies did not find evidence for an association (Fergusson et al., 1998), but the other study found evidence

for an association with heavier alcohol use (Larkby et al., 2011). Both of these studies were based on prospective longitudinal birth cohorts. Of the two other studies rated as very high risk of bias (2 points), one study on CD found a positive association with binge drinking (Whitbeck and Crawford, 2009) and other study based on ODD and using cross-sectional design did not find evidence for an association (Russell, Johnson, et al., 2015).

2.3.6.5 Association between caffeine consumption during pregnancy and ADHD and ODD in offspring

Out of the 56 studies, 3 investigated the association between maternal caffeine consumption during pregnancy and ADHD in offspring (N=3,627 to 24,156) (Del-Ponte et al., 2016; Kim et al., 2009; Linnet et al., 2009). Additionally, one study examined the association with ODD in offspring (N=5,924) (Russell, Johnson, et al., 2015). No evidence for a positive association was observed between maternal caffeine consumption during pregnancy and ADHD in offspring. Two of these studies used a longitudinal cohort design (Pelotas birth cohort in Brazil and the Aarhus birth cohort in Denmark) (Del-Ponte et al., 2016; Linnet et al., 2009) and one study used a case-control design in a Korean sample (Kim et al., 2009). A study of ODD based on a cross-sectional sample found a weak indication for an association with maternal prenatal caffeine use only in girls (Russell, Johnson, et al., 2015).

2.3.6.5.1 Strength of evidence based on NOS score

Two studies based on caffeine exposure and ADHD were rated as low risk of bias (8-9 points) (Del-Ponte et al., 2016; Linnet et al., 2009). Both studies did not find evidence for an association. One case-control study rated as high risk of bias (4 points) also did not find evidence for an association (Kim et al., 2009). Only one study on ODD rated as very high risk of bias (2 points) found a weak suggestive evidence for an association only in girls (Russell, Johnson, et al., 2015).

2.4 DISCUSSION

In this systematic review I examined whether there is evidence to support a causal effect of maternal smoking, alcohol and caffeine use during pregnancy on ADHD, CD and ODD risk in offspring by synthesising the results of existing research based on risk of bias assessment. Overall, my findings support stronger associations between prenatal smoking and ADHD and CD. However, evidence was less clear for the association with ODD and inconsistent on alcohol exposure in all the outcomes. My findings on caffeine exposure were limited to ADHD and there was lack of evidence for other outcomes.

My findings for smoking exposure indicate that maternal smoking during pregnancy is more strongly associated with ADHD and CD than with ODD. However, given that there are few studies on ODD, no strong conclusions can be drawn. Furthermore, some studies on ADHD with low risk of bias were able to take into account genetic effects, and indicate that shared genetics plays a substantial role in the association with prenatal smoking. This is supported by a previous study which used a genetically informed design and showed that the link between maternal prenatal smoking and offspring ADHD symptoms is likely to be inherited rather than due to intrauterine exposure (Thapar et al., 2009). Furthermore, another recent review concluded that besides ADHD, also the association between maternal prenatal smoking and CD symptoms could also be explained by familial confounding and shared genetics (Rice et al., 2018).

I identified relatively few studies that investigated the association between prenatal alcohol exposure and diagnosis of ADHD, CD and ODD in offspring. Evidence from these studies indicates that a stronger association exists between heavier alcohol consumption and ADHD and CD. A recent review and meta-analysis which investigated the association between maternal low to moderate alcohol consumption during pregnancy and ADHD in offspring did not find evidence for an increased risk of ADHD symptoms (Porter et al., 2019), but studies on CD symptoms using quasi-experimental designs have found evidence for a potential causal effect with maternal low

to moderate level alcohol consumption during pregnancy (D'Onofrio et al., 2007; Murray et al., 2016). Similarly, to alcohol exposure, I only identified a few studies on prenatal caffeine exposure and these studies do not provide evidence for a causal effect with ADHD.

However, several weaknesses and sources of heterogeneity between included studies emerged while I appraised the current research. First, included studies varied greatly on number of confounders adjusted in the multivariable analyses, thus raising the possibility of residual confounding. Although many studies adjusted for socioeconomic factors known to affect both exposures and outcomes, none of the studies adjusted for partner's substance use during pregnancy. There is evidence that assortative mating affects parental smoking and alcohol consumption and failure to take into account partner's substance use can lead to biased effect estimates (Madley-Dowd et al., 2020). Similarly, only a limited number of studies accounted for maternal mental health during pregnancy, which has also been found to be a potential risk factor. For example, it has been shown that maternal depressive and anxiety symptoms during pregnancy increased the risk for behavioural problems in offspring (Leis et al., 2014). In contrast, many studies on smoking exposure adjusted for perinatal factors, such as birth weight, gestational age or other pregnancy and birth complications, which could be potential mediators in the pathway between prenatal smoking and ADHD. Adjusting for mediators induces collider bias in unpredictable directions, as showed in previous studies (Schisterman et al., 2009). Therefore estimates adjusted for birth weight may result in spurious association if there is an unmeasured common cause between birth weight and outcome (Hernandez-Diaz et al., 2006).

Second, maternal prenatal exposure assessment was based on self-reports and mothers may under report their prenatal substance use, due to social desirability, which may lead to biased effect estimates in the studies. Furthermore, many studies assessed exposures after child's birth or retrospectively when the outcome was already present, which may lead to recall bias (this is the case for all included cross-sectional and for most case-

control studies). This means that from these studies causality should be interpreted cautiously. Third, studies also differed in terms of how prenatal smoking, alcohol and caffeine consumption were categorised. Many studies used a binary measure which does not adequately capture effects of substance use where these are dose-dependent. Some studies used a scale of low, moderate and high, but there is no clear definition what level of consumption each of these categories represent. Fourth, studies also varied on timing of substance use with the majority of studies using a single time point assuming that maternal substance use remains similar throughout pregnancy. One study on alcohol exposure reported that maternal prenatal alcohol consumption had a more harmful effect on offspring conduct disorder during the 1st trimester compared to the 3rd trimester indicating that prenatal alcohol exposure during the 1st pregnancy trimester may be more harmful (Larkby et al., 2011).

Fifth, considering that there is a high comorbidity between externalising disorders, only a few studies took this into account. Although high rates of comorbidity are common among psychiatric disorders, it is also plausible that somewhat different aetiology may underlie externalising disorders with comorbidities. For example, two studies that observed the association between maternal prenatal smoking and ADHD with comorbid conditions found that ADHD with comorbid CD/ODD had a stronger association with maternal prenatal smoking than ADHD without comorbidities (Arnold et al., 2005; Joelsson et al., 2016).

Sixth, although externalising disorders are more prevalent among boys than girls (Merikangas et al., 2009) few studies investigated gender effects. Some studies have shown that boys exposed to prenatal smoking and alcohol consumption may be at higher risk for developing behavioural problems than girls (Hutchinson et al., 2010; Niclasen et al., 2014) and it is possible that prenatal substance use may have distinct effects on boys and girls which needs more research.

Seventh, studies varied greatly on age when ADHD, CD and ODD were assessed. Although several studies have shown that childhood externalising disorder symptoms persist into adulthood (Kuja-Halkola et al., 2015; Reef et al., 2011), other studies have also found that childhood mental health problems change across development and persistence of externalising disorders also depends on severity and comorbidity of symptoms (Bunte et al., 2014; Caye et al., 2016). Furthermore, studies on ADHD have reported that presentation of hyperactive-impulsive and inattention symptoms varies from preschool to early adulthood and inattention symptoms tend to be more persistent (Dopfner et al., 2015). It is also suggested that child- and adulthood ADHD are two separate diagnoses and future studies should investigate which underlying mechanisms could explain these different developmental paths (Moffitt et al., 2015).

One major strength of this systematic review is including multiple prenatal exposures (smoking, alcohol and caffeine) and outcomes (ADHD, CD and ODD) which enabled me to synthesise whether the associations would differ across different exposure-outcome combinations. Additionally, conducting risk of bias assessments enabled me to account for the relative weaknesses in study designs when interpreting the evidence supporting a causal relationship.

However, this systematic review also has some limitations. First, I limited the searches to studies that used diagnosis as an outcome measure, and therefore I missed those studies reporting on symptoms scores or other continuous scales. Second, I only included English language studies. However, it has been shown that the exclusion of non-English studies has a little impact on overall findings (Morrison et al., 2012). Third, I was unable to quantitatively combine results into meta-analyses, due to the high degree of heterogeneity in exposure assessments, as well as study designs.

2.5 CHAPTER SUMMARY

My review showed that there is an association between maternal smoking during pregnancy and ADHD in offspring, but studies that accounted for

shared genetic and environmental confounders suggest that this association is unlikely to be causal. Given that majority of the identified studies investigated the association between ADHD and smoking exposure, findings with alcohol and caffeine exposures and CD and ODD need more research, especially using more genetically sensitive designs. Future studies should also use more prospective and quantitative exposure measures during each pregnancy trimester, as well as take into account comorbidities between externalising disorders, gender differences and changes in presentation and manifestation of externalising disorder symptoms across development.

In the next chapter, I describe cohorts used in my analyses to further investigate whether there is a causal effect of maternal smoking, alcohol and caffeine consumption during pregnancy on ADHD risk in offspring by using quasi-experimental designs.

Chapter 3 DESCRIPTIONS OF COHORTS

3.1 INTRODUCTION

In this thesis, I have used data from three longitudinal birth cohort studies: the Avon Longitudinal Study of Parents and Children (ALSPAC); the Generation R (GenR) and the Norwegian Mother, Father and Children Cohort Study (MoBa). In this chapter I will give an overview of each cohorts' participants, availability, quality control of genome-wide data, and assessment of exposures and outcome. I will also provide a comparison of parental socio-economic and exposure characteristics, as well as characteristics of outcomes in the children, between the cohorts. This chapter will end by describing the measures selected for analyses described in this thesis.

3.2 THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN (ALSPAC)

3.2.1 Cohort profile

ALSPAC is a prospective longitudinal cohort study designed to investigate genetic and environmental factors that influence health and development in parents and children (Fraser et al., 2013; Golding et al., 2001; Northstone et al., 2019).

To be eligible for the study, pregnant women had to be resident in the former county of Avon and their expected date of delivery had to be between 1st April 1991 and 31st December 1992. Women who were residents but left shortly after enrolment were excluded from further follow-up, but women who left the study area after completing the questionnaire in the 3rd pregnancy trimester were retained even if the baby was born after the move (Golding et al., 2001). The eligible sample consisted of 20,248 pregnancies and 14,676 participants were recruited during 1990-1992. More participants were recruited during campaigns when the children were aged 7 years old and between ages 8 and 18 years old. These campaigns resulted in a further 913 children who were enrolled into the study giving at total sample size of 15,454 pregnancies. After

excluding triplets and quadruplets, the final baseline sample size was 14,888 children (Northstone et al., 2019).

The Avon population was considered to be representative of Great Britain (GB) in terms of parents' ethnicity, marital status, higher education, and proportion of people living in rural areas. However, parents in ALSPAC were less likely to live in rented accommodation, and fathers were less likely to have a manual occupation compared with the rest of GB (Golding et al., 2001).

Data collection included self-reported questionnaires from mothers, their partners and their children from age 5 years; medical, educational and other records; interviews and examinations in the clinic, as well as measurements of biological and environmental samples (Boyd et al., 2013; Golding et al., 2001).

The ALSPAC study was approved by the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees and informed consent for the use of data collected via questionnaires and clinics was obtained from participants. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/

3.2.2 Genome-wide data and quality control

DNA samples were collected from 11,343 children and 10,015 mothers. ALSPAC children were genotyped using the Illumina HumanHap550 quad chip genotyping platforms. Individuals were excluded on the basis of gender mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%) and insufficient sample replication (identity-by-descent (IBD) <0.8). SNPs with a minor allele frequency of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium ($p < 10^{-7}$) were removed. Related subjects that passed all other quality control thresholds were retained during subsequent phasing and

imputation. A total of 9,115 children and 500,527 SNPs passed these quality control filters.

ALSPAC mothers were genotyped using the Illumina human660W-quad array at Centre National de Génotypage (CNG) and genotypes were called with Illumina GenomeStudio. SNPs were removed if they displayed more than 5% missingness or a Hardy-Weinberg equilibrium ($p < 10^{-6}$). Additionally, SNPs with a minor allele frequency of less than 1% were removed. Samples were excluded if they displayed more than 5% missingness, had indeterminate X chromosome heterozygosity or extreme autosomal heterozygosity.

Related subjects that passed all other quality control thresholds were retained during subsequent phasing and imputation. 9,048 mothers and 526,688 SNPs passed these quality control filters. Population stratification in mothers and children were compared with Hapmap II (release 22) European descent (CEU), Han Chinese, Japanese and Yoruba reference populations; all individuals with non-European ancestry were removed.

After combining genotype data in the mothers and the children, SNPs with genotype missingness above 1% were removed due to poor quality (11,396 SNPs removed) and a further 321 subjects were removed due to potential ID mismatches. This resulted in a dataset of 17,842 subjects. Imputation of the target data was performed using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3) (all polymorphic SNPs excluding singletons), using all 2,186 reference haplotypes (including non-Europeans). After imputation and filtering on MAF > 0.01 and info > 0.8 8,282,911 SNPs remained in the dataset.

The final dataset included 8,237 children and 8,196 mothers.
More details about the genotyping and quality control procedure can be found elsewhere (Paternoster et al., 2011; Taylor, Jones, et al., 2018).

3.2.3 Assessment of ADHD

3.2.3.1 The Development And Well-Being Assessment (DAWBA)

The DAWBA is a semi-structured interview administered to parents of children aged 4-16 years, to adolescents over 11 years, and a briefer questionnaire administered to teachers. The DAWBA was designed to bring together information from different sources (Goodman et al., 2000). Additionally, a computer algorithm is used to generate diagnoses called "DAWBA bands" which are based on the symptoms and impact reported in the DAWBA. The DAWBA bands can be generated for both informant-specific and multi-informant measures, and these have been found to be a useful complement for clinician-rated diagnoses (Goodman et al., 2011). The DAWBA covers disorders such as separation anxiety, specific and social phobias, post-traumatic stress-disorder, obsessive compulsive disorder, generalised anxiety disorder, major depression, ADHD, conduct and oppositional-defiant disorder. However, teachers are not asked in detail about children's internalising disorder symptoms and children are not asked in detail about their own externalising disorder symptoms (Loeber et al., 1991).

The ADHD subscale consists of 18 items that measure total symptoms of ADHD and 9 items that separately measure inattentive and hyperactive-impulsive symptom domains. The 18 items are made up of 9 items of inattentive symptoms and 9 items of hyperactive-impulsive symptoms. The items assess degree of symptom on Likert scales ranging from 0-2: 0 = no more than other; 1 = a little more than others; and 2 = a lot more than others.

The DAWBA can be used either by a trained interviewer or it can be self-completed online or via questionnaire (Goodman et al., 2011). The DAWBA has been found to be a reliable measure for distinguishing children with mental health problems both in clinical and community population (Foreman et al., 2009; Goodman et al., 2000).

In ALSPAC, ADHD was measured using the maternal report of DAWBA at age 7.5, 10, 13 and 15.5 years, and the teacher report is available at age 7 and 10 years. The DAWBA bands are available at age 7.5 and 15.5 years. In the analyses I used maternal and teacher reported ADHD subscale at age 7 years.

3.2.3.2 The Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a brief behavioural screening questionnaire for children and adolescents at age 3-16 years completed by parents and teachers (Goodman, 1997). The questionnaire has 25 items which are divided into five subscales: emotional symptoms, conduct problems, hyperactivity problems, peer problems and prosocial behaviour. The hyperactivity subscale covers both hyperactivity and inattention symptoms. The items assess presence of symptoms on Likert scales ranging from 0-2: 0 = not true; 1 = somewhat true; and 2 = certainly true. The SDQ has been used in both clinical and community settings and has been found to be a good measure for identifying children with a higher risk of mental disorders (Goodman, 1997). Although the instrument is widely used, psychometric properties are poorer with respect to sensitivity than specificity, and when only a single-informant rater is used (Goodman, 1997; Goodman et al., 2003).

In ALSPAC, maternal reported SDQ is available at age 4, 7, 8, 10, 12, 13 and 16.5 years and teacher reports at ages 7 and 10 years. In this thesis I used the hyperactivity subscale at age 7 years.

3.2.3.3 Descriptive statistics of ADHD measures

Although data from multiple timepoints were available, descriptive statistics are shown at age around 7-8, as data at this timepoint were available across the cohorts. Analyses were conducted in the full sample without stratifying the sample by gender as there were few ADHD cases among girls after accounting for exposure and confounder data. In the analyses, both maternal and teacher reports were used. Descriptive statistics of ADHD measures with maternal and teacher report after accounting for missing items are given in Tables 3.1 and 3.2.

The sample size varied depending on the instrument used and whether ADHD symptoms were assessed by parents or teachers. Children assessed with maternal reported DAWBA scale were on average 7.7 years old, 6.8 years old when ADHD symptoms were assessed with SDQ scale and 8.3 years old when ADHD symptoms were reported by teachers. The total available sample size where any items were answered was 8,005 when maternal reported DAWBA scale was used, 8,267 when SDQ scale was used and 6,222 when teacher reported DAWBA and SDQ scales were used. However, analyses were performed accounting for four missing items for total ADHD symptoms, two missing items for hyperactive-impulsive and inattentive symptoms and one missing item when SDQ scale was used. Missing items were accounted for by calculating row mean scores which was used as an outcome measure. Accounting for missing items when questionnaire data has been used, has been applied before in psychology research (Forand and DeRubeis, 2013; Hazel et al., 2014).

The distribution of maternal and teacher reported ADHD symptoms based on row mean scores are shown in Figures 3.1 and 3.2.

Scores were zero-inflated and therefore binary variables were derived using 85 percentile threshold of total symptoms and separately for hyperactive-impulsive and inattentive symptoms to represent the children with the greatest number of symptoms. Although maternal reported ADHD symptoms score measured with SDQ was not zero-inflated and the distribution was right-skewed, a binary variable was derived using the same threshold for consistency.

As shown in Table 3.1, in total there were 1,152 children above the 85th percentile threshold with higher risk for more severe ADHD symptoms, 1,015 children with more severe hyperactivity symptoms and 1,088 children with more severe inattention symptoms rated with maternal reported DAWBA scale. 909 children were above the 85th percentile threshold with maternal reported SDQ scale. The proportion of children with higher risk for

more severe ADHD, hyperactive-impulsive and inattention symptoms were similar with teacher reported DAWBA and SDQ scales (Table 3.2).

Correlations between maternal and teacher reported ADHD symptom scales together with the sample sizes are shown in Table 3.3. The correlation between ADHD total symptoms and hyperactive-impulsive and inattention symptom domains with maternal reported DAWBA scale was similar for both symptom domains (r = 0.93) but somewhat higher with inattention symptom domain on the teacher reported DAWBA scale (r_{INA} = 0.94; r_{HYP} = 0.87).

The correlation between maternal reported DAWBA and SDQ scales was moderate (r = 0.63), but higher in teacher reported DAWBA and SDQ scales (r = 0.90). Furthermore, the correlation between maternal and teacher reported DAWBA and SDQ scales was low (r_{DAWBA} = 0.47; r_{SDQ} = 0.41) indicating that mothers and teachers may report different aspects of ADHD.

Table 3.1. Descriptive statistics of maternal reported ADHD symptoms scales in ALSPAC

Measure	Total available sample size	Sample size in analyses	Gender (boys/girls)	Child age (Mean, SD)	Total number of items	Number of missing items allowed	Row mean score	SD	85% cut-off score	Children above the cut-off (boys/girls)
ADHD (DAWBA)	8,005	7,913	4,054/3,859	7.5-9.3 years (7.7, 0.14)	18	4	0.275	0.380	0.611	1,152 (14.56%) (787/365)
HYPERACTIVE	7,996	7,933	4,069/3,864	7.5-9.3 years (7.7, 0.14)	9	2	0.274	0.405	0.667	1,015 (12.79%) (688/327)
INATTENTIVE	7,978	7,922	4,057/3,865	7.5-9.3 years (7.7, 0.14)	9	2	0.277	0.413	0.667	1,088 (13.73%) (739/349)
ADHD (SDQ)	8,267	8,148	4,186/3,962	6.7-8.4 years (6.8, 0.11)	5	1	0.677	0.473	1.2	909 (11.16%) (606/303)

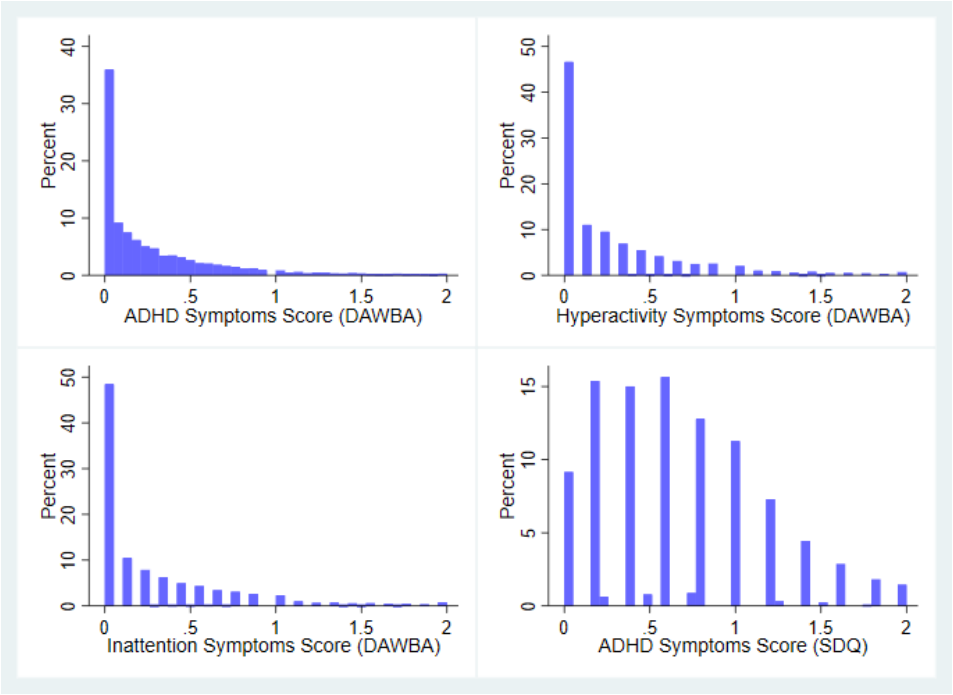
Note: Development And Well-Being Assessment (DAWBA), Strengths and Difficulties Questionnaire (SDQ), SD – standard deviation

Table 3.2. Descriptive statistics of teacher reported ADHD symptoms scales in ALSPAC

Measure	Total available sample size	Sample size in analyses	Gender (boys/girls)	Child age (Mean, SD)	Total number of items	Number of missing items allowed	Row mean score	SD	85% cut-off score	Children above the cut-off (boys/girls)
ADHD (DAWBA)	6,214	6,210	3,132/3,078	7.7-9.5 years (8.3, 0.31)	19	4	0.353	0.441	0.789	911 (14.67%) (717/194)
HYPERACTIVE	6,213	6,209	3,131/3,078	7.7-9.5 years (8.3, 0.31)	9	2	0.213	0.413	0.556	813 (13.09%) (656/157)
INATTENTIVE	6,214	6,210	3,133/3,077	7.7-9.5 years (8.3, 0.31)	10	2	0.479	0.546	1.1	807 (13%) (616/191)
ADHD (SDQ)	6,222	6,207	3,131/3,076	7.7-9.5 years (8.3, 0.31)	5	1	0.538	0.544	1.2	717 (11.55%) (569/148)

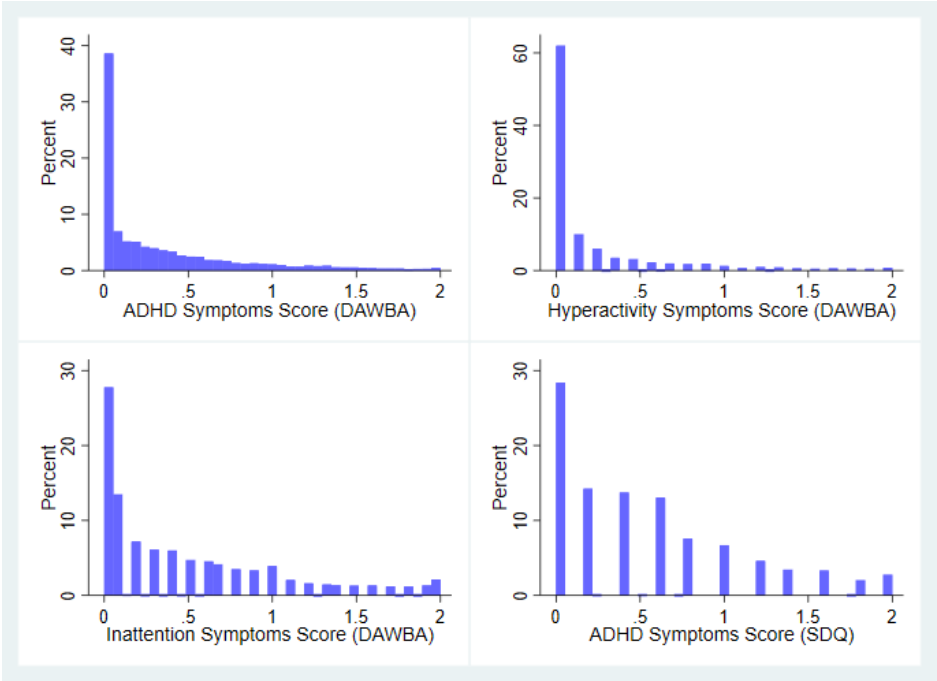
Note: Development And Well-Being Assessment (DAWBA), Strengths and Difficulties Questionnaire (SDQ), SD – standard deviation

Figure 3.1. Distribution of ADHD symptoms score with maternal reported DAWBA and SDQ scales in ALSPAC



Note: Development And Well-Being Assessment (DAWBA), Strengths and Difficulties Questionnaire (SDQ)

Figure 3.2. Distribution of ADHD symptoms score with teacher reported DAWBA and SDQ scales in ALSPAC



Note: Development And Well-Being Assessment (DAWBA), Strengths and Difficulties Questionnaire (SDQ)

Table 3.3. Correlation matrix between maternal and teacher reported ADHD symptoms scales in ALSPAC

	ADHD (DAWBA)	HYPERACTIVE (DAWBA)	INATTENTIVE (DAWBA)	ADHD (SDQ)	ADHD (TR DAWBA)	HYPERACTIVE (TR DAWBA)	INATTENTIVE (TR DAWBA)	ADHD (TR SDQ)
ADHD (DAWBA)	1.00 (N=7,913)							
HYPERACTIVE (DAWBA)	0.928 (N=7,900)	1.00 (N=7,933)						
INATTENTIVE (DAWBA)	0.930 (N=7,893)	0.726 (N=7,880)	1.00 (N=7,922)					
ADHD (SDQ)	0.634 (N=7,009)	0.597 (N=7,028)	0.580 (N=7,019)	1.00 (N=8,148)				
ADHD (TR DAWBA)	0.474 (N=3,846)	0.422 (N=3,858)	0.456 (N=3,852)	0.404 (N=3,973)	1.00 (N=6,210)			
HYPERACTIVE (TR DAWBA)	0.413 (N=3,845)	0.416 (N=3,857)	0.350 (N=3,851)	0.323 (N=3,972)	0.870 (N=6,209)	1.00 (N=6,209)		
INATTENTIVE (TR DAWBA)	0.442 (N=3,846)	0.362 (N=3,858)	0.456 (N=3,852)	0.398 (N=3,973)	0.942 (N=6,208)	0.653 (N=6,207)	1.00 (N=6,210)	
ADHD (TR SDQ)	0.467 (N=3,844)	0.412 (N=3,856)	0.453 (N=3,850)	0.412 (N=3,970)	0.896 (N=6,197)	0.744 (N=6,196)	0.868 (N=6,196)	1.00 (N=6,207)

Note: Development And Well-Being Assessment (DAWBA), Strengths and Difficulties Questionnaire (SDQ), Teacher report (TR)

3.2.4 Assessment of parental prenatal substance use

Maternal and paternal smoking, alcohol and caffeine use during pregnancy were measured at 18 weeks of gestation. Additionally, mothers were asked about their consumption behaviour at 8 and 32 weeks of gestation. The questionnaire "Your Environment" was designed to collect measures around early pregnancy (approximately 8 weeks of gestation), this was administered at enrolment to pregnant women who joined the study before 23 weeks gestation. The range of gestational ages were from 6-28 weeks. The 32 weeks gestation questionnaire ("Having a baby") was sent out to mothers in the study at 32 weeks, for mother's enrolling after 32 weeks gestation the questionnaire was sent out at enrolment. The range of gestational ages covered by this questionnaire were from 32-40 weeks.

An overview of exposure assessments in mothers and fathers is given in Table 3.4.

Table 3.4. Maternal and paternal exposure assessment in ALSPAC

MOTHER
8 weeks of gestation
Smoking
Number of cigarettes currently smoked per day
Alcohol consumption
Alcoholic drinks consumed during the week and weekend
Caffeine consumption
Number of cups of tea and coffee consumed per day (caffeinated and decaffeinated)
18 weeks of gestation
Smoking
Have ever been a smoker
What age started smoking regularly
Stopped smoking during pregnancy
Number of cigarettes smoked before pregnancy, first 3 months of pregnancy and past 2 weeks
Exposure to passive smoke at home and work
Partner's current smoking status

Number of cigarettes partner smokes
Alcohol consumption*
Amount of alcohol consumption (in units) before current pregnancy, during first 3 months of pregnancy and at the time when they first felt the baby move, per day/week Number of days consumed at least 4 units of alcohol in one occasion Amount of partner's average alcohol consumption (in units) per day/week
Caffeine consumption**
Number of cups of coffee, tea and cola consumed per day during the week and weekend Type of drink consumed (caffeinated, decaffeinated or both)
FATHER
Smoking
Have ever been a smoker Age started smoking Stopped smoking during partner's pregnancy Number of cigarettes smoked at the start of their partner's pregnancy and in the last 2 weeks
Alcohol consumption
Amount of alcohol consumption before their partner's pregnancy and first 3 months of their partner's pregnancy, units per day/week Number of days had more than 4 units of alcohol in the past month
Caffeine consumption
Number of cups of caffeinated and decaffeinated coffee and tea consumption per day Number of cups of cola consumption per week
32 weeks of gestation
MOTHER
Smoking
Number of cigarettes per day currently smoking Time exposed to passive smoke
Alcohol consumption
Average alcohol consumption in units during week and weekend Number of days consumed at least 4 units of alcohol in one occasion
Caffeine consumption

Number of cups of caffeinated and decaffeinated coffee, tea and cola drinking per day

**1 unit or 1 drink of alcohol is equivalent to 8 grams of alcohol*
***caffeine consumption was transformed into milligrams of caffeine in a day. In ALSPAC, caffeine transformation has been used for a cup of coffee 75mg; a cup of tea 40mg and a can of cola 33mg*

3.2.4.1 Descriptive statistics of parental socio-demographic characteristics and prenatal substance use

Overview of maternal and paternal socio-demographic characteristics and substance use during the 1st pregnancy trimester in the full and analysis sample is given in Table 3.5.

Visual comparisons of maternal and paternal smoking, alcohol and caffeine consumption during the 1st pregnancy trimester in the full sample are presented in Appendices 3.1-3.3.

The mean age of mothers at child's birth in the full sample was 28 years and in fathers 30 years. In the analysis sample mothers were on average a year older (mean age at child's birth 29 years).

In the full sample, the majority of participants were Europeans (~97%) and married (75%), but the proportion of mothers who were married was even higher in the analysis sample (81%).

Comparing maternal and paternal educational qualifications in the full sample, there were more fathers with the Certificate of Secondary Education (CSE) level and degree level education (22% and 21%) than mothers (20% and 13%). However, O-level qualification was more frequent in mothers (35%) compared to fathers (22%). Compared to the full sample, the proportion of mothers and fathers with degree level education was higher in the analysis sample (16% of mothers and 23% of fathers) and fewer parents with the CSE level education remained to the study (14% of mothers and 18% of fathers).

In terms of social class distribution (based on the Office of Population Censuses and Surveys in the UK), in the full sample more fathers had a higher social class (47%) compared to mothers (37%) and this proportion was even higher in the analysis sample (51% of fathers and 41% of mothers with I and II level). Whereas more mothers had skilled non-manual occupation (43%) than fathers (11%). However, nearly 4,000 mothers did not report about their social class.

Comparing parental mental health in the full and analysis sample, the proportion of mothers who screened positive for depression and anxiety was lower in the analysis sample. The proportion was more similar among fathers.

Comparing maternal and paternal prenatal substance use in the full and analysis sample, there were more mothers and fathers who reported no smoking in the analysis sample (81% of mothers and 70% of fathers) than in the full sample (75% of mothers and 66% of fathers). As well as the proportion of mothers and fathers who reported smoking >10 cigarettes per day was smaller in the analysis sample (9% of mothers and 21% of fathers) than in the full sample (14% of mothers and 25% of fathers). Proportion of mothers and fathers consuming alcohol were similar in the full and analysis sample but proportion of mothers who reported higher caffeine consumption (>300mg/day) was a bit smaller in the analysis sample (21%) than in the full sample (24%). However, more than 2,000 fathers did not report about their prenatal consumption behaviour.

Overview of maternal and paternal smoking, alcohol and caffeine consumption correlations in the full and analysis sample is given in Tables 3.6 and 3.7.

Overall, correlations between maternal and paternal prenatal substance use in the full and analysis sample were similar. The highest correlation in the analysis sample was between maternal prenatal smoking and caffeine consumption ($r = 0.24$), whereas the correlation between paternal prenatal

smoking and caffeine consumption was 0.12. The correlation between maternal prenatal smoking and alcohol consumption was 0.12 which in fathers was 0.01. The correlation between alcohol and caffeine consumption was similar in mothers (r = 0.09) and fathers (r = 0.07).
The highest correlation between maternal and paternal substance use was in smoking (r = 0.37). Correlation between parental alcohol consumption was 0.22 and parental caffeine consumption 0.19. These correlations indicate that mothers smoke and consume less alcohol and caffeine during pregnancy than fathers.

Table 3.5. Maternal and paternal socio-demographic characteristics and substance use in the 1st pregnancy trimester in the full and analysis sample in ALSPAC

	Mothers (full sample)	Mothers (analysis sample)	Fathers (full sample)	Fathers (analysis sample)
Sample size	N=13,697	N=7,886	N=9,999	N=6,608
Age (child's birth)	(15-44 years) *Mean* 28 years; *SD* 4.98	(15-44 years) *Mean* 29 years; *SD* 4.61	(16-75 years) *Mean* 30 years; *SD* 6.71	(16-75 years) *Mean* 30 years; *SD* 6.54
Ethnicity				
European	11,747 (97%)	7,500 (98%)	9,455 (97%)	6,346 (97%)
Non-European	314 (3%)	131 (2%)	329 (3%)	168 (3%)
Missing data	1,636	255	215	94
Education*				
CSE	2,454 (20%)	1,094 (14%)	2,159 (22%)	1,174 (18%)
Vocational	1,200 (10%)	678 (9%)	804 (8%)	518 (8%)
O level	4,206 (35%)	2,699 (35%)	2,080 (22%)	1,391 (22%)
A level	2,732 (22%)	1,965 (26%)	2,638 (27%)	1,840 (29%)
Degree	1,560 (13%)	1,219 (16%)	1,965 (21%)	1,507 (23%)
Missing data	1,545	231	353	178
Social class**				
I	583 (6%)	465 (7%)	1,074 (12%)	834 (14%)
II	3,090 (31%)	2,229 (34%)	3,197 (35%)	2,296 (37%)
III (non-manual)	4,212 (43%)	2,798 (43%)	1,022 (11%)	734 (12%)
III (manual)	774 (8%)	429 (6%)	2,704 (30%)	1,666 (27%)
IV	969 (10%)	527 (8%)	838 (9%)	472 (8%)
V	217 (2%)	111 (2%)	244 (3%)	142 (2%)
Missing data	3,852	1,327	920	464
Marital status				
Never married	2,449 (19%)	1,079 (14%)		
Widowed	18 (0,10%)	9 (0.1%)		
Divorced/separated	755 (6%)	372 (4.9%)		
Married	9,612 (74.9%)	6,267 (81%)		

Missing data	863	159		
Financial difficulties	11,826	7,455		
	Mean 2.9; *SD* 3.53	*Mean* 2.55; *SD* 3.32		
Missing data	1871	431		
Depression				
Screened positive	1,637 (14%)	811 (11%)	282 (4%)	176 (3%)
Screened negative	10,268 (86%)	6,455 (89%)	7,345 (96%)	5,182 (97%)
Missing data	1,792	620	2,372	1,250
Anxiety				
Screened positive	1,930 (16%)	1,010 (14%)	817 (11%)	549 (10%)
Screened negative	9,867 (84%)	6,198 (86%)	6,805 (89%)	4,803 (90%)
Missing data	1,900	678	2377	1,256
Smoking				
No cigarettes	9,675 (75%)	6,256 (81%)	4,783 (66%)	3,566 (70%)
1-4 cigarettes	684 (5%)	372 (5%)	361 (5%)	263 (5%)
5-9 cigarettes	726 (6%)	367 (5%)	297 (4%)	210 (4%)
>10 cigarettes	1,762 (14%)	736 (9%)	1,827 (25%)	1,072 (21%)
Missing data	850	155	2,731	1,497
Alcohol consumption				
Never	5,786 (45%)	3,411 (44%)	302 (4%)	179 (3%)
<1 drink a week	4,946 (39%)	3,119 (40%)	1,756 (23%)	1,197 (23%)
>1 drink a week	1,776 (14%)	1,046 (14%)	3,912 (52%)	2,802 (53%)
1+ drink a day	244 (2%)	135 (2%)	1,554 (21%)	1,114 (21%)
Missing data	945	175	2,475	1,316
Caffeine consumption				
0-49mg	1,705 (13%)	1,026 (13%)	268 (4%)	186 (3%)
50-199mg	4,950 (39%)	3,149 (41%)	984 (13%)	668 (13%)
200-299mg	3,065 (24%)	1,871 (25%)	1,185 (15%)	848 (16%)
>300mg	2,992 (24%)	1,634 (21%)	5,185 (68%)	3,648 (68%)
Missing data	985	206	2,377	1,258

**CSE reflects to the certificate of secondary education. O level is equivalent to grades D and E and A level is equivalent to grades A to C after GCSE examination. Degree level reflects to higher education diploma **Social class levels are based on individual's occupation: I–professional; II–managerial and technical; III–skilled non-manual; IV–partly skilled; V-unskilled*

Table 3.6. Maternal and paternal substance use correlation matrix in the full sample in ALSPAC

	Maternal smoking	Maternal alcohol	Maternal caffeine	Paternal smoking	Paternal alcohol	Paternal caffeine
Maternal smoking	1.00					
	12,873					
Maternal alcohol	0.122	1.00				
	12,724	12,777				
Maternal caffeine	0.250	0.106	1.00			
	12,686	12,620	12,737			
Paternal smoking	0.399	0.045	0.147	1.00		
	9,178	9,145	9,103	9,242		
Paternal alcohol	-0.053	0.220	-0.008	-0.007	1.00	
	9,472	9,445	9,399	9,074	9,537	
Paternal caffeine	0.042	0.025	0.174	0.125	0.073	1.00
	9,645	9,595	9,557	9,190	9,481	9,713

Table 3.7. Maternal and paternal substance correlation matrix in the analysis sample in ALSPAC

	Maternal smoking	Maternal alcohol	Maternal caffeine	Paternal smoking	Paternal alcohol	Paternal caffeine
Maternal smoking	1.00					
	7,731					
Maternal alcohol	0.118	1.00				
	7,691	7,711				
Maternal caffeine	0.244	0.091	1.00			
	7,660	7,646	7,680			
Paternal smoking	0.373	0.043	0.146	1.00		
	5,924	5,914	5,889	5,945		
Paternal alcohol	-0.010	0.220	0.005	0.012	1.00	
	6,133	6,124	6,096	5,858	6,155	
Paternal caffeine	0.037	0.017	0.188	0.124	0.071	1.00
	6,211	6,199	6,172	5,919	6,125	6,234

3.3 THE GENERATION R (GENR)

3.3.1 Cohort profile

The Generation R (GenR) is a population-based prospective cohort study in Rotterdam in the Netherlands designed to investigate environmental and genetic causes of health and development from fetal life until young adulthood. GenR recruited 9,778 pregnant women who were expected to give birth between April 2002 and January 2006 in Rotterdam. Of all eligible pregnant women, 61% agreed to participate in the study. The final baseline sample size included 9,749 children and 80% of the sample has been followed up until age 13 years. The GenR is a multi-ethnic cohort. Besides Dutch ethnicity, other largest ethnic groups making up the GenR cohort are Surinamese, Turkish and Moroccan. In terms of representativeness of the study population, parents in GenR had a higher socio-economic status compared with the general population in the Netherlands.

Data collection in GenR included self-reported questionnaires, interviews, physical examinations, behavioural observations, as well as magnetic resonance imaging (MRI) and biological samples (Jaddoe et al., 2006; Kooijman et al., 2016).

The GenR study was approved by the local Medical Ethical Committee (MEC 198.782/2001/31). Written informed consent was obtained from all participating women.

3.3.2 Genome-wide data and quality control

Genotype data were either collected from cord blood at birth (Illumina 610K Quad Chip) for 5,908 children (Generation R-1) and for additional 320 samples blood sample were collected by venipuncture (Illumina 660K Quad Chip) during a visit to the research centre at age 6 years (Generation R-2). Variants were filtered for minor allele frequency (MAF < 0.01), Hardy-–Weinberg disequilibrium ($p < 10^{-7}$) and missing rate (> 0.05). Individuals

were additionally filtered on relatedness, sex mismatch and a total of 178 samples with genotyping rates lower than 97.5 % were excluded from the final projects (Generation R-1 and Generation R-2 sets). The combined dataset, merged using only SNPs common to both platforms (n = 5,809), consisted of 549,511 SNPs. Imputation was based on two different reference panels: HapMap Project Phase II Release 22, build 36 phasing and 1000 Genomes Project (phase III release version), build 37 phasing. After imputation and restricting on MAF < 0.01 18,804,120 SNPs were included.

Individuals from European descent were selected within 4 standard deviations on the first four genetic principal components of the HapMap Phase II Northwestern European (CEU) population. The final genome-wide data is available for 5,732 children from different ethnic backgrounds and for 2,661 children from the European ethnicity.

Currently (as of 2nd March 2020) maternal genotype data is not available yet and is going through quality control procedure. More details about the genotyping procedure and quality control can be found elsewhere (Medina-Gomez et al., 2015).

3.3.3 Assessment of ADHD

3.3.3.1 The revised Conners' Parent Rating Scale (CPRS-R)

The CPRS-R was developed for screening and assessing child's behavioural problems based on parental report (Conners et al., 1998). The CPRS-R has full and short versions. The full CPRS-R comprises seven subscales: cognitive, oppositional, hyperactive-impulsive, anxious-shy, perfectionism, psychosomatic and social problems. The hyperactive-impulsive subscale consists of nine items and the cognitive problems subscale twelve items which are rated on 4-point Likert scale (0 = not at all true to 3 = very much true). The short version comprises four subscales: oppositional, cognitive problems/inattention, hyperactivity and ADHD index, which was included to detect children with an ADHD diagnosis (Kao and Thomas, 2010).

The CPRS-R has both maternal and teacher report and the instrument has been found to be good for distinguishing ADHD symptom domains (inattention and hyperactive-impulsive), identifying children with higher risk of ADHD diagnosis and monitoring treatment outcomes in clinical settings (Conners et al., 1998; Gianarris et al., 2001).

In GenR, maternal report of the CPRS-R was used in the analyses at age 7.5 years.

3.3.3.2 The Child Behavior Checklist (CBCL)

The CBCL (now called the *Achenbach System of Empirically Based Assessment*) provides information on child's behavioural problems and social competencies (Achenbach, 1991). The CBCL has two versions: the preschool questionnaire for children at age 1.5 to 5 years and school-age questionnaire for children and adolescents at age 6 to 18 years. The CBCL has 8 subscales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour and aggressive behaviour. These are further divided into two broader groups: internalising and externalising problems (Achenbach, 1991). Attention problems subscale consists of 5 items in the preschool version and 10 items in the school-age version. These are rated using a 3-point scale: 0 = not true; 1 = somewhat true; and 2 = very true.

The CBCL also provides DSM-IV oriented scales associated with anxiety, oppositional defiant disorder, conduct problems, somatic problems, affective problems, and attention deficit disorder. The CBCL has parental, teacher (Teacher Report Form (TRF)) and children's self-report version (Youth Self-Report (YSR)). The CBCL has been widely used in different cultural settings with good psychometric properties (Achenbach et al., 2008).

In GenR, maternal report has been used at age 1.5, 3, 6, 7.5, 9 and 14 years. Teacher report is available at age 7 years and children's own self-report at age 9 and 14 years. In the analyses I used maternal and teacher report of attention problems subscale at age 6 and 7 years.

3.3.3.3 Descriptive statistics of ADHD measures

Descriptive statistics of ADHD measures with maternal and teacher report after excluding siblings and accounting for missing items is given in Table 3.8.

The mean age of children assessed with maternal reported CPRS-R scale was 8.2 years. Children were on average 6.1 years old when ADHD symptoms were assessed with CBCL and 6.7 years old when TRF was used. The total available sample size where any items were answered when assessed with the CPRS-R scale was 4,589, 6,142 when assessed with CBCL scale and 4,609 when TRF was used.

However, I performed the analyses accounting for up to three missing items for total ADHD symptoms, two missing items for hyperactive-impulsive and inattention symptoms measured with CPRS-R, one missing item when CBCL scale was used and four missing items were allowed with TRF. Missing items were accounted for by calculating weighted sum scores for each scale.

The distribution of ADHD symptoms measured with CPRS-R, CBCL and TRF is shown in Figure 3.3.

Scores were mostly zero-inflated, except total ADHD symptoms score measured with CPRS-R which was right-skewed. Therefore, as in ALSPAC, I derived binary variables using 85 percentile threshold of total symptoms and separately for hyperactive-impulsive and inattentive symptoms to represent these children with the higher risk for ADHD symptoms.

As shown in Table 3.8, there were 549 children above the 85th percentile threshold with higher risk for more severe ADHD symptoms, 477 children with more severe hyperactive-impulsive symptoms and 424 children with more severe inattention symptoms rated with CPRS-R scale. 750 children were above the 85th percentile threshold with CBCL scale and 623 with TRF.

Correlations between the scales used for assessing ADHD symptoms together with the sample sizes are shown in Table 3.9.

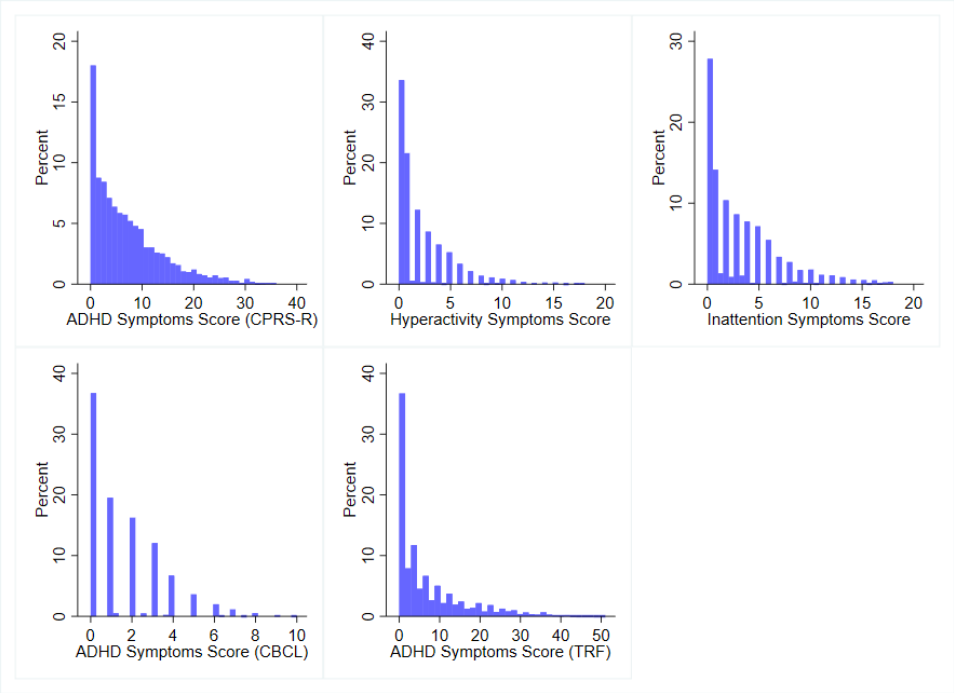
The correlation with ADHD total symptoms was higher for inattention symptoms domain (r = 0.89), compared to hyperactive-impulsive symptoms domain (r = 0.72). The correlation between maternal reported CPRS-R and CBCL scales was moderate (r = 0.55) but lower between CPRS-R and TRF (r = 0.37). Furthermore, the correlation was even lower between TRF and CPRS-R hyperactive-impulsive symptom domain (r = 0.30) and somewhat higher between TRF and CPRS-R inattention symptom domain and CBCL scale (r = 0.36). This indicates differences depending on the instrument and rater used for assessing ADHD symptoms.

Table 3.8. Descriptive statistics of ADHD symptoms scales in GenR

Measure	Total available sample size	Sample size in analysis	Gender (boys/girls)	Child age (Mean, SD)	Total number of items	Number of missing items allowed	Mean score	SD	85% cut-off score	Children above the cut-off (boys/girls)
ADHD (CPRS-R)	4,589	3,849	1,911/1,938	7.5-10.8 years (8.2, 0.23)	18	3	7.24	6.63	14	549 (13.9%) (345/204)
HYPERACTIVE	4,587	3,853	1,913/1,940	7.5-10.8 years (8.2, 0.23)	9	2	2.13	2.72	5	477 (10.6%) (300/177)
INATTENTIVE	4,589	3,854	1,911/1,943	7.5-10.8 years (8.2, 0.23)	9	2	3.15	3.38	7	424 (12.1%) (268/156)
CBCL	6,142	5,183	2,601/2,582	4.9-9.1 years (6.1, 0.49)	5	1	1.54	1.74	3	750 (13.5%) (464/286)
TRF	4,609	3,952	2,003/1,949	4.2-9.97 years (6.7, 1.30)	25	4	6.79	8.78	15	623 (15%) (464/159)

Note: Revised Conners' Parent Rating Scale (CPRS-R), Child Behavior Checklist (CBCL), Teacher Report Form (TRF), SD – standard deviation

Figure 3.3. Distribution of ADHD symptoms score measured with CPRS-R, CBCL and TRF scales in GenR



Note: Revised Conners' Parent Rating Scale (CPRS-R), Child Behavior Checklist (CBCL), Teacher Report Form (TRF)

Table 3.9. Correlation matrix between ADHD symptoms scales in GenR

	ADHD (CPRS-R)	HYPERACTIVE (CPRS-R)	INATTENTIVE (CPRS-R)	ADHD (CBCL)	ADHD (TRF)
ADHD (CPRS-R)	1.00				
	3,849				
HYPERACTIVE (CPRS-R)	0.719	1.00			
	3,847	3,854			
INATTENTIVE (CPRS-R)	0.889	0.571	1.00		
	3,845	3,850	3,853		
ADHD (CBCL)	0.552	0.535	0.443	1.00	
	3,606	3,611	3,610	5,184	
ADHD (TRF)	0.369	0.298	0.359	0.363	1.00
	2,105	2,108	2,108	2,870	3,952

Note: Revised Conners' Parent Rating Scale (CPRS-R), Child Behavior Checklist (CBCL), Teacher Report Form (TRF)

3.3.4 Assessment of parental prenatal substance use

Maternal smoking, alcohol and caffeine consumption during pregnancy were measured in each pregnancy trimester. Paternal smoking and alcohol consumption were assessed in the 2nd pregnancy trimester only.
An overview of parental exposure assessment is given in Table 3.10.

Table 3.10. Maternal and paternal exposure assessment in GenR

MOTHER
<18 weeks of gestation
Smoking
Stopped or continued smoking during pregnancy
Number of cigarettes smoked before pregnancy and in the past 3 months of pregnancy
Time exposed to passive smoke at home and work
Partner's current smoking status before pregnancy
Number of cigarettes partner smoked before pregnancy
Alcohol consumption*
Number of glasses of alcohol consumed before pregnancy and in the past 3 months of pregnancy (per week/day)
Number of days consumed more than 6 glasses a day in the past 3 months
Number of glasses of alcohol partner consumed before pregnancy (per week/day)
Caffeine consumption**
Number of cups of coffee and tea consumed per day in the past 3 months
Type of drink consumed (caffeinated, decaffeinated or both)
18-25 weeks of gestation
MOTHER
Smoking
Number of cigarettes smoked in the past 2 months
Time exposed to passive smoke at home and work
Alcohol consumption
Number of glasses of alcohol consumed in the past 2 months (per week/month)
Number of days consumed more than 6 glasses a day in the past 2 months

Caffeine consumption
Number of cups of coffee and tea consumed daily before pregnancy and in the past 2 months of pregnancy
Type of drink consumed (caffeinated, decaffeinated or both)
FATHER
Smoking
Number of cigarettes smoked 2 months before their partner's pregnancy
Alcohol consumption
Number of glasses of alcohol consumed per week or day 2 months before their partner's pregnancy
Number of days consumed more than 6 glasses a day in the past 6 months
>25 weeks of gestation
MOTHER
Smoking
Number of cigarettes smoked in the past 2 months
Time exposed to passive smoke at home and work
Alcohol consumption
Number of classes of alcohol consumed in the past 2 months per week/month
Number of days consumed more than 6 glasses a day in the past 2 months
Caffeine consumption
Number of cups of coffee and tea consumed daily before pregnancy and in the past 2 months of pregnancy

** A measure of alcoholic drink is based one glass containing 12g of pure alcohol*
***Paternal caffeine consumption was not assessed. Maternal caffeine consumption was assessed from coffee and tea and transformed into milligrams a day based on that 125ml coffee contains 90mg of caffeine, decaffeinated coffee 3mg and a cup of tea 45mg*

3.3.4.1 Descriptive statistics of parental socio-demographic characteristics and prenatal substance use

An overview of maternal and paternal socio-demographic characteristics and substance use during the 1st pregnancy trimester in the full and analysis sample is given in Table 3.11.

Visual comparisons of maternal and paternal smoking and alcohol consumption during the 1st pregnancy trimester in the full sample is presented in Appendices 3.4 and 3.5.

The mean age of mothers at study intake in the full sample was 30 years and in fathers 33 years. In the analysis sample mothers and fathers were a year older (mean age in mothers 31 years and in fathers 34 years).

Nearly 60% of mothers and fathers in the full sample were Europeans. Other major ethnic groups were Moroccan, Surinamese and Turkish (nearly 25% of mothers and fathers in these ethnic groups). However, the proportion of mothers and fathers with European ethnicity was bigger in the analysis sample (71% of mothers and 78% of fathers).

86% of mothers were married or cohabiting and 14% were single in the full sample, but the proportion of mothers either married or cohabiting was higher in the analysis sample (91%).

In terms of education, in the full sample, 43% of mothers and 51% of fathers had a higher education, 46% of mothers and 41% of fathers had a secondary education and 11% of mothers and 8% of fathers had a primary education. However, the proportion of mothers and fathers with higher education was larger in the analysis sample (54% mothers and 57% of fathers) and smaller with primary education (6% mothers and 5% fathers). Furthermore, mothers who reported having financial difficulties in the full sample (22%) were less likely to remain in the study (15% in the analysis sample).

Comparing parental mental health in the full and analysis sample, the proportion of mothers who screened positive for depression and anxiety was lower in the analysis sample. The proportion was more similar among fathers. However, nearly 3,000 mothers and over 2,000 fathers did not report about their mental health status.

The proportion of mothers and fathers who reported no smoking was similar in the full and analysis sample (analysis sample: 79% of mothers and 59% of fathers; full sample: 75% of mothers and 56% of fathers). However, mothers and fathers who reported smoking were less likely to remain in the study (25% of mothers in the full sample compared to 20% in the analysis sample and 44% of fathers in the full sample compared to 41% in the analysis sample).

The proportion of mothers and fathers who reported no drinking was slightly lower in the analysis sample compared to the full sample (57% of mothers in the full sample and 49% in the analysis sample and 17% of fathers in the full sample and 12% in the analysis sample). Similarly, the proportion of mothers who reported lower caffeine consumption (<49mg/day) was smaller in the analysis sample (19%) compared to the full sample (23%). More than 2,000 mothers and fathers did not report their smoking and alcohol consumption.

An overview of maternal and paternal smoking, alcohol and caffeine consumption correlations in the full and analysis sample is given in Tables 3.12 and 3.13.

Overall, correlations between maternal and paternal prenatal substance use in the full and analysis sample were similar. The highest correlation in the analysis sample were between maternal prenatal alcohol and caffeine consumption (r = 0.21) and maternal smoking and caffeine consumption (r = 0.16). The correlation between maternal prenatal smoking and alcohol consumption was 0.14. The correlation between maternal and paternal alcohol consumption was 0.39 and maternal and paternal smoking 0.36. The correlation between paternal smoking and alcohol consumption was 0.07.

Table 3.11. Maternal and paternal socio-demographic characteristics and substance use in the 1st pregnancy trimester in the full and analysis sample in GenR

	Mothers (full sample)	Mothers (analysis sample)	Fathers (full sample)	Fathers (analysis sample)
	N=9,504	N=3,849	N=7,323	N=2,672
Age (study intake)	15-46 years *Mean* 29.9; *SD* 5.4	15-46 years *Mean* 31.4; *SD* 4.8	14-68 years *Mean* 33; *SD* 6	17-58 years *Mean* 33.8; *SD* 5.3
Ethnicity				
European	5,128 (58%)	2,715 (71%)	4,791 (59%)	2,073 (78%)
Moroccan	599 (7%)	145 (4%)	584 (7%)	57 (2%)
Surinamese	783 (9%)	210 (5%)	678 (9%)	130 (5%)
Turkish	779 (9%)	234 (6%)	681 (8%)	108 (4%)
Others	1,555 (17%)	521 (14%)	1,401 (17%)	303 (11%)
Missing data	662	24	960	1
Education				
Primary	939 (11%)	232 (6%)	423 (8%)	132 (5%)
Secondary	3,833 (46%)	1,444 (40%)	2,116 (41%)	921 (38%)
Higher	3,560 (43%)	1,968 (54%)	2,602 (51%)	1,366 (57%)
Missing data	1,174	205	2,182	253
Marital status				
Married	4,161(50%)	1,894 (51%)		
Cohabiting	2,983 (36%)	1,452 (40%)		
Single	1,199 (14%)	330 (9%)		
Missing data	1,234	173		
Financial difficulties				
No difficulties	4,995 (78%)	2,607 (85%)		
Some difficulties	1,148 (18%)	405 (13%)		
Great difficulty	268 (4%)	58 (2%)		
Missing data	3,095	779		
Depression				
Screened positive	683 (10%)	213 (7%)	171 (3%)	62 (3%)

Screened negative	5,855 (90%)	2,787 (93%)	4,713 (97%)	2,294 (97%)
Missing data	2,968	849	2,439	316
Anxiety				
Screened positive	765 (12%)	267 (9%)	344 (7%)	144 (6%)
Screened negative	5,778 (88%)	2,734 (91%)	4,551 (93%)	2,213 (94%)
Missing data	2,963	848	2,428	315
Smoking				
No cigarettes	5,550 (75%)	2,471 (79%)	2,809 (56%)	1,412 (59%)
1-4 cigarettes	962 (13%)	358 (12%)	779 (16%)	387 (16%)
5-9 cigarettes	478 (7%)	159 (5%)	441 (9%)	166 (7%)
>10 cigarettes	359 (5%)	128 (4%)	946 (19%)	416 (18%)
Missing data	2,157	733	2,348	291
Alcohol consumption				
None	4,202 (57%)	1,521 (49%)	854 (17%)	279 (12%)
<1 drink a week	1,860 (25%)	933 (30%)	713 (14%)	311 (13%)
>1 drink a week	1,137 (16%)	576 (18%)	2,259 (46%)	1,166 (49%)
1+ drink a day	176 (2%)	97 (3%)	1,131 (23%)	617 (26%)
Missing data	2,131	722	2,366	299
Caffeine consumption				
0-49mg	1,395 (23%)	499 (19%)		
50-199mg	2,850 (47%)	1,251 (48%)		
200-299mg	951 (16%)	443 (17%)		
>300mg	875 (14%)	420 (16%)		
Missing data	3,435	1,236		

Table 3.12. Maternal and paternal substance use correlation matrix in the full sample in GenR

	Maternal smoking	Maternal alcohol	Maternal caffeine	Paternal smoking	Paternal alcohol
Maternal smoking	1.00				
	7,349				
Maternal alcohol	0.127	1.00			
	7,276	7,375			
Maternal caffeine	0.173	0.201	1.00		
	5,955	5,978	6,071		
Paternal smoking	0.349	-0.025	0.066	1.00	
	4,477	4,491	3,725	4,975	
Paternal alcohol	0.060	0.420	0.128	0.078	1.00
	4,464	4,479	3,711	4,921	4,957

Table 3.13. Maternal and paternal substance use correlation matrix in the analysis sample in GenR

	Maternal smoking	Maternal alcohol	Maternal caffeine	Paternal smoking	Paternal alcohol
Maternal smoking	1.00				
	2,446				
Maternal alcohol	0.140	1.00			
	2,428	2,455			
Maternal caffeine	0.164	0.209	1.00		
	2,026	2,032	2,056		
Paternal smoking	0.364	0.018	0.069	1.00	
	2,170	2,180	1,825	2,381	
Paternal alcohol	0.061	0.390	0.144	0.072	1.00
	2,165	2,175	1,821	2,360	2,373

3.4 THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY (MOBA)

3.4.1 Cohort profile

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study in Norway with an aim to investigate factors influencing health and disease exposures and outcomes throughout the life course. MoBa study began in July 1999 where pregnant women were invited to participate until December 2008. After the initial recruitment phase, fathers were also invited to participate in the study. All pregnant women in Norway were eligible to participate and out of 277,702 pregnancies, the participation rate was 41% (Magnus et al., 2016). The cohort includes more than 114,000 children, 95,000 mothers and 75,000 fathers across Norway. Additionally, about 16,400 families with two or more pregnancies were included. However, it has been reported that women <25 years, those living alone, and smokers were underrepresented indicating selection bias in the MoBa study (Nilsen et al., 2009).

Data collection included self-reported questionnaires, biological and environmental samples. Furthermore, all residents in Norway have a unique identification number that enables researchers to link the collected data with various health registries, such as Medical Birth Registry, National Patient Registry and Prescription Database (Magnus et al., 2016).

Informed consent was obtained from all study participants. The administrative board of the Norwegian Mother, Father, and Child Cohort Study led by the Norwegian Institute of Public Health approved the study protocol. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committee for Medical Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The study was approved by The Regional Committee for Medical Research Ethics (#2012/67).

3.4.2 Genome-wide data and quality control

Approximately 17,000 trios from the Norwegian Mother, Father and Child cohort were genotyped in three batches. The first batch, comprising 20,664 individuals and 542,585 SNPs, was genotyped at the Genomics Core Facility (Iceland) using the Illumina HumanCoreExome (Illumina, San Diego, USA) genotyping array, version 12 1.1. The second batch, comprising 12,874 individuals and 547,644 SNPs was genotyped at the Genomics Core Facility (Iceland) using the Illumina HumanCoreExome (Illumina, San Diego, USA) genotyping array, version 24 1.0. The third batch, comprising 17,949 individuals and 692,367 SNPs, was genotyped at ERASMUS MC (the Netherlands) using the Illumina Global Screening Array (Illumina, San Diego, USA) version 24 1.

Individuals were excluded if they had a genotyping call rate below 95% or autosomal heterozygosity greater than four standard deviations from the sample mean. SNPs were excluded if they were ambiguous (A/T and C/G), had a genotyping call rate below 98%, minor allele frequency of less than 1%, or Hardy-Weinberg equilibrium P-value less than 1×10^{-6}. Relatedness was assessed by flagging one individual from each pairwise comparison of IBD with a pi-hat greater than 0.1.

Population stratification was assessed, using the HapMap phase 3 release 3 as a reference by principal component analysis using EIGENSTRAT version 6.1.4. Visual inspection identified a homogenous population of European ethnicity and individuals of non-European ethnicity were removed.

Duplicate samples were removed, and each genotyping batch was split into parents and offspring. Quality control (QC) was then conducted by genotyping array in parents and offspring separately.

The parents and offspring datasets were then merged into one dataset per genotyping batch, keeping only the SNPs that passed quality control in both datasets. All individuals passing the genotyping call rate and autosomal heterozygosity measures were included in the merged datasets. Therefore,

the merged datasets included individuals previously excluded or flagged as a duplicate, ethnic outlier, having a sex discrepancy, or high level of relatedness. Concordance checks were then conducted on validated duplicates. Duplicate, tri-allelic and discordant (any discordance between the validated duplicates) SNPs were excluded. Individuals and SNPs with a genotyping call rate below 98% in the merged datasets were excluded. The duplicate sample that was removed before the start of the quality control was then excluded. Mendelian errors identified by the assessment of duos and trios were then recoded to missing. Insertions and deletions were also excluded.

After QC the Human Core Exome 12 batch comprised 20,231 individuals and 384,855 SNPs, the Human Core Exome 24 batch comprised 12,757 individuals and 396,189 SNPs, and the Global Screening Array batch comprised 17,742 individuals and 568,275 SNPs. Imputation was conducted separately for each genotyping batch by using the Haplotype reference consortium (HRC) release 1-1 as the genetic reference panel.

Post imputation quality control was performed by removing individuals if they had a genotyping call rate less than 99% or were of non-European ethnicity. After quality control, a core homogeneous sample of European ethnicity (based on principal components analysis (PCA) of markers overlapping with available HapMap markers, unrelated (within generation, defined as accumulated IBD <0.015 and overall IBD PI_HAT <10%) individuals across all batches and arrays were available for use in analysis ($N_{children}$ = 15,208; $N_{mothers}$ = 14,804; $N_{fathers}$ = 15,198) and in total 5,003,747 SNPs were included after post imputation.

More details about the genotyping and quality control procedure have been reported elsewhere (Helgeland et al., 2019).

3.4.3 Assessment of ADHD

Selected items from the shorter form of CBCL was used at age 1.5, 3 and 5 years and the CPRS-R short version at age 5 years. More details about both

of the instruments can be found in the section 3.3.3 (“Assessment of ADHD in GenR”).

3.4.3.1 The Parent/Teacher Rating Scale for Disruptive Behavior Disorders (RS-DBD)

The RS-DBD was developed to assess oppositional-defiant disorder, conduct disorder and ADHD using both parental and teacher ratings. The scale consists of 41 DSM-IV oriented items for measuring these three distinctive externalising disorders. The ADHD subscale consists of 18 items which are rated on a 4-point Likert scale: 1 = not at all; 2 = just a little; 3 = pretty much; and 4 = very much (Silva et al., 2005).

In MoBa, currently maternal report is available at age 8 years. In this thesis I used only RS-DBD scale as other scales were used at the younger age.

3.4.3.2 Descriptive statistics of ADHD measure

Descriptive statistics of ADHD measure are given in Table 3.14. The mean age of children assessed with maternal reported RS-DBD scale was 8.2 years. The total available sample size where any items were answered was 43,512. The maximum sample size used in analyses was 43,451. As in ALSPAC, analyses were performed accounting for four missing items for total ADHD symptoms, two missing items for hyperactive-impulsive and inattentive symptoms by calculating row mean scores.

The distribution of ADHD symptoms based on row mean scores is shown in Figure 3.4.

The distribution of ADHD symptoms was right-skewed and to keep consistency with ALSPAC and GenR cohorts, I derived binary variables by using 85 percentile threshold of total symptoms and separately for hyperactive-impulsive and inattentive symptoms. There were 5,808 children with higher risk for more severe ADHD symptoms, 5,738 children with more severe hyperactivity symptoms and 5,082 children with more severe inattention symptoms.

The correlation matrix between ADHD symptom domains is given in Table 3.15.

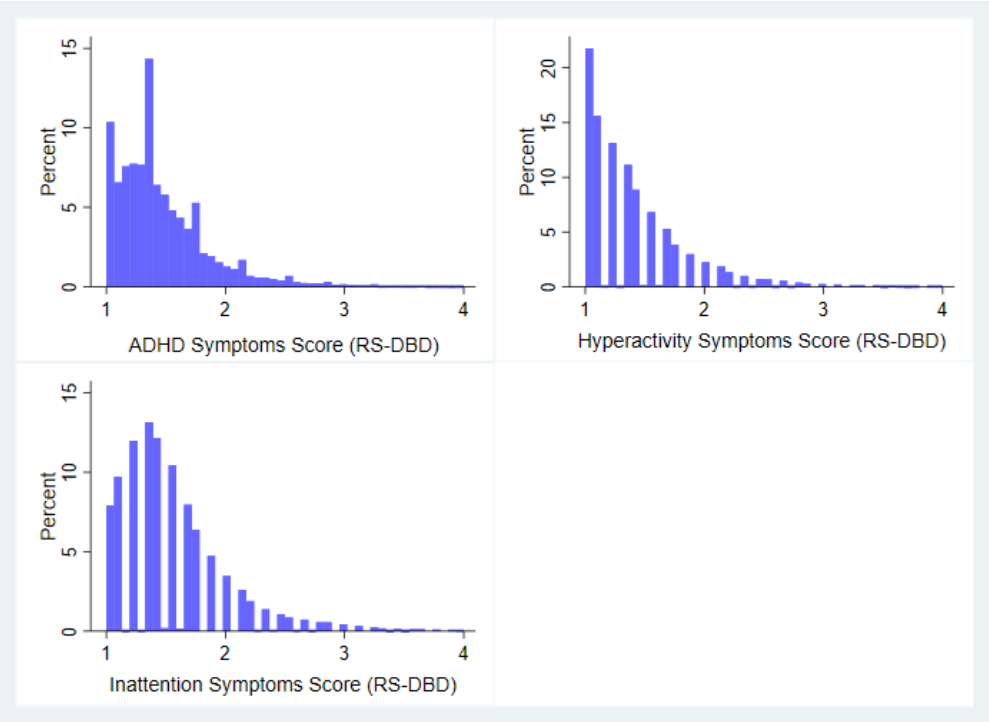
The correlation was high between ADHD total symptoms and hyperactive-impulsive (r = 0.89) and inattention symptom domains (r = 0.90) but was lower between hyperactive-impulsive and inattention symptom domains (r = 0.61). This indicates that RS-DBD scale is capturing different symptom domains of ADHD.

Table 3.14. Descriptive statistics of maternal reported ADHD symptoms scales in MoBa

Measure	Total available sample size	Sample size in analysis	Gender (boys/girls)	Child age (Mean, SD)	Total number of items	Number of missing items allowed	Row mean score	SD	85% cut-off score	Children above the threshold (boys/girls)
ADHD (RS-DBD)	43,512	43,441	22,115/21,249	7.9-10.3 years (8.2, 0.17)	18	4	1.474	0.401	1.833	5,808 (13.37%) (3,870/1,938)
HYPERACTIVE	43,500	43,433	22,109/21,247	7.9-10.3 years (8.2, 0.17)	9	2	1.396	0.434	1.777	5,738 (13.21%) (3,683/2,055)
INATTENTIVE	43,467	43,451	22,127/21,247	7.9-10.3 years (8.2, 0.17)	9	2	1.553	0.460	2	5,082 (11.70%) (3,369/1,713)

Note: Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Figure 3.4. Distribution of ADHD symptoms score with the maternal reported RS-DBD scale in MoBa



Note: Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Table 3.15. Correlation matrix of ADHD subscales measured with the RS-DBD scale in MoBa

	ADHD	HYPERACTIVE	INATTENTIVE
ADHD (RS-DBD)	1.00		
	43,441		
HYPERACTIVE	0.891	1.00	
	43,424	43,433	
INATTENTIVE	0.904	0.611	1.00
	43,424	43,407	43,451

Note: Rating Scale for Disruptive Behavior Disorders (RS-DBD)

3.4.4 Assessment of parental prenatal substance use

Maternal smoking and alcohol consumption during pregnancy were measured at 17 and 30 weeks of gestation and 6 months after the child's birth. Caffeine consumption during pregnancy was measured at 17 and 30 weeks of gestation.

Paternal smoking, alcohol and caffeine consumption was assessed at 17 weeks of gestation.

Overview of maternal and paternal exposure assessment is given in Table 3.16.

Table 3.16. Maternal and paternal exposure assessment in MoBa

MOTHER
17 weeks of gestation
Smoking
Have ever been a smoker
Stopped smoking after becoming pregnant
Number of cigarettes smoked per day and week before pregnancy and after pregnancy was known
Exposure to passive smoke at home and work
Partner's current smoking status
Alcohol consumption*
Frequency and number of units of alcohol consumed 3 months before pregnancy and during pregnancy per week/month
Frequency of drinking 5 alcohol units or more at least once in the last 3 months before pregnancy and during pregnancy
Caffeine consumption**
Number of cups/glasses of caffeinated and decaffeinated coffee, tea and cola consumption per day
FATHER
Smoking
Have ever been a smoker
Number of cigarettes smoked 6 months before their partner's pregnancy and after their partner become pregnant
Alcohol consumption

Ever drunk alcohol Frequency and number of units of alcohol consumed 6 months before partner's pregnancy and after partner become pregnant per week/month Frequency of drinking 5 alcohol units or more at least one occasion 6 months before partner's pregnancy and after partner become pregnant
Caffeine consumption
How often consumed coffee, tea and cola weekly and daily
30 weeks of gestation
MOTHER
Smoking
Number of cigarettes per day currently smoking Exposure to passive smoke at home and work Partner's smoking status Number of cigarettes partner smokes per day
Alcohol consumption
Frequency and number of units of alcohol consumed 3 months before pregnancy, 0-12 weeks of pregnancy, 13-24 weeks of pregnancy and 25+ weeks of pregnancy per week/month Frequency of drinking 5 alcohol units or more at least once 3 months before pregnancy, 0-12 weeks of pregnancy, 13-24 weeks of pregnancy and 25+ weeks of pregnancy
Caffeine consumption
Number of cups/glasses of caffeinated and decaffeinated coffee, tea and cola drinking per day after the 13th week of pregnancy
6 months after the child's birth
MOTHER
Smoking
Number of cigarettes per day smoked last 3 months of pregnancy Number of cigarettes per day partner smoked last 3 months of pregnancy
Alcohol consumption
Frequency and number of units of alcohol consumed last 3 months of pregnancy per week/month

**A measure of alcoholic unit and 1 drink was equivalent to 12.8 grams of pure alcohol; **Caffeine consumption into milligrams a day was transformed based on a cup of boiled/filtered coffee contains 85mg of caffeine, instant/espresso coffee 60mg; a cup of tea 50mg and soft drinks 30mg of caffeine*

3.4.4.1 Descriptive statistics of parental socio-demographic statistics and prenatal substance use

An overview of maternal and paternal socio-demographic characteristics and substance use during the 1st pregnancy trimester in the full and analysis sample is given in Table 3.17.

Visual comparisons of maternal and paternal smoking, alcohol and caffeine consumption during the 1st pregnancy trimester in the full sample are presented in Appendices 3.6-3.8.

The mean age of mothers at child's birth in the full sample was 30 years and in fathers 33 years, whereas in the analysis sample mothers were a year older (mean age at child's birth 31 years). The majority of participants were married or cohabiting (96%).

Comparing maternal and paternal education in the full sample, mothers were more highly educated (64%) than fathers (51%). The proportion of mothers and fathers with higher education was even higher in the analysis sample (72% of mothers and 56% of fathers). Further, 17% of mothers reported having financial difficulties in the full sample comparing with 14% in the analysis sample, but more than 22,000 mothers did not report financial difficulties at the initial assessment.

In terms of parental mental health, 8% of mothers screened positive for depression and anxiety problems in the full sample and 6% in the analysis sample. Among fathers the proportion who screened positive for depression and anxiety problems was similar in the full and analysis sample (3%). The proportion of mothers and fathers who screened positive for more severe ADHD symptoms was similar in the full and analysis sample (3% in mothers and 5% in fathers). However, there is a substantial degree of missing data at the time parental ADHD was assessed (child age at 5 years).

Comparing maternal and paternal prenatal substance use in the full and analysis sample, the proportion of mothers and fathers who reported no smoking was similar in the analysis sample (94% of mothers and 79% of fathers) and in the full sample (92% of mothers and 77% of fathers). Likewise, proportions in the maternal and paternal alcohol and caffeine consumption were similar in the full and analysis sample although more than 21,000 mothers and nearly 50,000 fathers did not report their alcohol consumption.

An overview of maternal and paternal smoking, alcohol and caffeine consumption correlations in the full and analysis samples is given in Tables 3.18 and 3.19.

Overall, correlations between maternal and paternal prenatal substance use in the full and analysis samples were similar.

In the analysis sample, the highest correlations were between maternal prenatal smoking and caffeine consumption (r = 0.19) and maternal prenatal alcohol and caffeine consumption (r = 0.17). Whereas correlation between maternal prenatal smoking and alcohol consumption was 0.04.

In fathers, the correlation between prenatal alcohol and caffeine consumption was higher (r = 0.24) than between prenatal smoking and caffeine consumption (r = 0.13) and prenatal smoking and alcohol consumption (r = 0.05). The highest correlation between maternal and paternal prenatal substance use was in smoking (r = 0.29) and was more similar in alcohol (r = 0.15) and caffeine consumption (r = 0.13).

Table 3.17. Maternal and paternal socio-demographic characteristics and substance use in the 1st pregnancy trimester in the full and analysis sample in MoBa

	Mothers (full sample)	Mothers (analysis sample)	Fathers (full sample)	Fathers (analysis sample)
	N=114,143	N=43,364	N=77,648	N=35,376
Age (child's birth)*	16-46 years (Mean 30; SD 4.65)	16-46 years (Mean 31; SD 4.41)	17-60 years (Mean 33; SD 5.32)	17-60 years (Mean 33; SD 5.20)
Education				
Primary	2,803 (3%)	587 (1%)	2,982 (4%)	1,078 (3%)
Secondary	32,451 (33%)	10,859 (27%)	33,338 (45%)	13,872 (41%)
Higher	63,004 (64%)	29,506 (72%)	38,446 (51%)	19,072 (56%)
Missing data	16,399	2,412	3,033	1,356
Marital status				
Married	49,800 (48%)	21,699 (51%)	38,246 (49%)	18,374 (52%)
Cohabiting	49,785 (48%)	19,949 (46%)	37,985 (49%)	16,426 (46%)
Single	2,413 (3%)	724 (2%)	929 (%)	334 (1%)
Other	1,024 (1%)	371 (1%)	639 (1%)	242 (1%)
Missing data	11,635	621	508	
Financial difficulties				
Yes	15,977 (17%)	5,888 (14%)		
No	76,572 (83%)	35,132 (86%)		
Missing data	22,108	2,409		
Depression/Anxiety				
Screened positive	8,198 (8%)	2,617 (6%)	2,633 (3%)	1,038 (3%)
Screened negative	94,631 (92%)	40,008 (94%)	74,634 (97%)	34,151 (97%)
Missing data	11,828	739	532	189
Parental ADHD				
Screened positive	1,664 (3%)	877 (3%)	1,740 (5%)	720 (5%)
Screened negative	54,888 (97%)	33,961 (97%)	32,789 (95%)	14,877(95%)
Missing data	58,105	8,526	43,600	19,781
Smoking				

No cigarettes	94,566 (92%)	40,266 (94%)	59,014 (77%)	27,537 (79%)
1-4 cigarettes	4,093 (4%)	1,284 (3%)	7,441 (10%)	3,302 (9%)
5-9 cigarettes	2,510 (2%)	664 (2%)	2,271 (3%)	905 (3%)
>10 cigarettes	1,950 (2%)	457 (1%)	8,085 (10%)	2,981 (9%)
Missing data	11,538	693	1,510	653
Alcohol consumption				
None	82,078 (88%)	34,645 (88%)	4,646 (16%)	1,955 (15%)
<1 drink a week	10,767 (11.55%)	4,464 (11.55%)	7,692 (27%)	3,511 (27%)
>1 drink a week	380 (0.44%)	165 (0.44%)	10,089 (36%)	4,734 (36%)
1+ drink a day	9 (0.01)	3 (0.01%)	5,922 (21%)	2,856 (22%)
Missing data	21,423	4,087	49,697	22,322
Caffeine consumption				
0-49mg	75,653 (66%)	27,347 (63%)	8,142 (24%)	3,500 (22%)
50-199mg	31,429 (28%)	13,192 (30%)	12,265 (35%)	5,610 (36%)
200-299mg	4,946 (4%)	1,907 (5%)	10,002 (29%)	4,617 (30%)
>300mg	2,615(2%)	917 (2%)	4,221 (12%)	1,915 (12%)
Missing data	14	1	43,495	19,736

**In mothers lower and upper age was coded <17 and >45; in fathers lower and upper age was coded <18 and >59*

Table 3.18. Maternal and paternal substance use correlation matrix in the full sample in MoBa

	Maternal smoking	Maternal alcohol	Maternal caffeine	Paternal smoking	Paternal alcohol	Paternal caffeine
Maternal smoking	1.00					
	103,119					
Maternal alcohol	0.045	1.00				
	92,927	93,234				
Maternal caffeine	0.222	0.165	1.00			
	103,105	93,225	114,643			
Paternal smoking	0.324	0.007	0.081	1.00		
	75,692	68,703	76,801	76,811		
Paternal alcohol	-0.039	0.141	0.103	0.028	1.00	
	27,956	25,465	28,345	28,108	28,349	
Paternal caffeine	0.018	0.056	0.133	0.120	0.243	1.00
	34,140	30,719	34,627	34,142	25,213	34,630

Table 3.19. Maternal and paternal substance use correlation matrix in the analysis sample in MoBa

	Maternal smoking	Maternal alcohol	Maternal caffeine	Paternal smoking	Paternal alcohol	Paternal caffeine
Maternal smoking	1.00					
	42,740					
Maternal alcohol	0.042	1.00				
	39,184	39,277				
Maternal caffeine	0.192	0.172	1.00			
	42,739	39,276	43,440			
Paternal smoking	0.286	0.015	0.069	1.00		
	34,688	31,936	34,948	34,949		
Paternal alcohol	-0.011	0.146	0.115	0.050	1.00	
	13,087	12,072	13,170	13,066	13,170	
Paternal caffeine	0.023	0.044	0.127	0.126	0.240	1.00
	15,680	14,355	15,782	15,555	11,828	15,782

3.5 COHORT COMPARISON

A comparison of the cohorts' parental socio-demographic characteristics and substance use during the 1st pregnancy trimester in the analysis sample is given in Table 3.20. The comparison of the cohorts' child characteristics is given in Table 3.21.

In general, the majority of participants were married but mothers and fathers in GenR and MoBa were somewhat older at their child's birth than in ALSPAC.

In terms of ethnicity, parents in ALSPAC and MoBa were mostly Europeans but in GenR, 29% of mothers and 22% of fathers were Non-Europeans. Likewise, in GenR and MoBa parents were more highly educated comparing with parents in ALSPAC.

However, mothers in ALSPAC reported having more financial difficulties (60%) compared to mothers in GenR (15%) and MoBa (14%). Furthermore, mothers and fathers in ALSPAC had more depression and anxiety symptoms compared to mothers and fathers in GenR and MoBa.

In terms of parental prenatal substance use, mothers in MoBa smoked and consumed less alcohol and caffeine during pregnancy compared to mothers in ALSPAC and GenR.

Maternal smoking during pregnancy was more similar in ALSPAC (19%) and GenR (20%) but mothers in ALSPAC reported drinking more alcohol during pregnancy (56%) than mothers in GenR (51%). Similarly, 21% of mothers in ALSPAC consumed more than 300mg of caffeine per day, compared to mothers in GenR (16%).

Among children, gender distribution was similar in all the cohorts but in GenR and MoBa children were slightly older (8.2 years) compared to

children in ALSPAC (7.6 years) when ADHD symptoms were assessed using a scale that measures hyperactive-impulsive and inattention symptom domains.

Furthermore, the proportion of first-born children was higher in GenR (61%) compared to ALSPAC and MoBa (46%).

Table 3.20. Comparison of cohorts' parental socio-demographic characteristics and parental substance use during the 1st pregnancy trimester in the analysis sample

	ALSPAC		GenR		MoBA	
Characteristics	**Mothers**	**Fathers**	**Mothers**	**Father**	**Mothers**	**Fathers**
N	7,886	6,608	3,849	2,672	43,364	35,376
Mean age at child's birth	(29 years)	(30 years)	(31 years)	(34 years)	(31 years)	(33 years)
Ethnicity*						
European	7,500 (98%)	7,311 (97%)	2,715 (71%)	2,073 (78%)	41,196 (95%)	33,607 (95%)
Non-European	131 (2%)	216 (3%)	1,110 (29%)	598 (22%)	2,168 (5%)	1,769 (5%)
Marital status						
Married	6,267 (81%)		1,894 (51%)		21,699 (51%)	
Cohabiting	-		1,452 (40%)		19,949 (46%)	
Single	381 (5%)		330 (9%)		724 (2%)	
Other	1,079 (14%)				371 (1%)	
Education						
Primary	1,094 (14%)	1,513 (20%)	232 (6%)	132 (5%)	587 (1%)	1,088 (3%)
Secondary	5,342 (70%)	4,320 (58%)	1,444 (40%)	921 (38%)	10,859 (27%)	13,961 (41%)
Higher	1,219 (16%)	1,591 (22%)	1,968 (54%)	1,366 (57%)	29,506 (72%)	19,190 (56%)
Financial difficulties**						
Yes	4,448 (60%)		463 (15%)		5,888 (14%)	
No	3,007 (40%)		2,607 (85%)		35,132 (86%)	
Mental health***						
Depression	811 (11%)	220 (4%)	213 (7%)	62 (3%)	2,664 (3%)	1,044 (3%)
Anxiety	1,010 (14%)	649 (10%)	267 (9%)	144 (6%)		
Smoking						
No cigarettes	6,256 (81%)	4,032 (68%)	2,471 (79%)	1,412 (59%)	40,335 (94%)	27,715 (79%)
1-4 cigarettes	372 (5%)	302 (5%)	358 (12%)	387 (16%)	1,284 (3%)	3,321 (9%)
5-9 cigarettes	367 (5%)	261 (4%)	159 (5%)	166 (7%)	664 (2%)	908 (3%)
>10 cigarettes	736 (9%)	1,350 (23%)	128 (4%)	416 (18%)	457 (1%)	3,005 (9%)
Alcohol consumption						
None	3,411 (44%)	229 (4%)	1,521 (49%)	279 (12%)	34,645 (88%)	1,966 (15%)

<1 unit per week	3,119 (40%)	1,429 (23%)	933 (30%)	311 (13%)	4,464 (11.5%)	3,530 (27%)
1-6 units per week	1,046 (14%)	3,218 (52%)	576 (18%)	1,166 (49%)	165 (0.44%)	4,785 (36%)
>1 unit per day	135 (2%)	1,279 (21%)	97 (3%)	617 (26%)	3 (0.01)	2,889 (22%)
Caffeine consumption						
0-49mg per day	1,026 (13%)	225 (4%)	499 (19%)		27,424 (63%)	3,529 (22%)
50-199mg per day	3,149 (41%)	785 (13%)	1,251 (48%)		13,192 (30%)	5,661 (36%)
200-299mg per day	1,871 (25%)	970 (15%)	443 (17%)		1,907 (5%)	4,661(30%)
>300mg per day	1,634 (21%)	4,254 (68%)	420 (16%)		917 (2%)	1,931(12%)

** In MoBa, participants are 95% Scandinavians and 5% non-scandinavians; **In ALSPAC, financial difficulties were measured with 5 items questionnaire: 1) Difficulty in affording food; 2) Difficulty in affording clothing; 3) Difficulty in affording heating 4) Difficulty in affording accommodation 5) Difficulty in affording things for baby. In GenR, financial difficulties were assessed with single item question: Difficulty in paying food, rent, bills and suchlike. In MoBa, financial difficulties were assessed with single item question: Have you experienced financial problems?; In MoBa, depression and anxiety symptoms were assessed together*

Table 3.21. Comparison of cohorts' child characteristics and maternal reported ADHD cases above the 85th percentile threshold

	ALSPAC	GENR	MOBA
N	7,850	3,849	43,512
Age	7.5 – 9 years (*Mean* = 7.6, *SD* 0.14)	7.5-11 years *(Mean* = 8.2, *SD* 0.23)	8-10 years, (*Mean* = 8.2; *SD* 0.17)
Gender			
Male	4,054 (51%)	1,911 (50%)	22,115(51%)
Female	3,859 (49%)	1,938 (50%)	21,249 (49%)
Parity			
1st	3,533 (46%)	2,278 (61%)	19,788 (46%)
2nd	2,735 (36%)	1,019 (28%)	15,339 (35%)
3rd	1,017 (13%)	309 (8%)	6,522 (15%)
4th+	361 (5%)	100 (3%)	1,715 (4%)
Proportion of children with ADHD symptoms above the 85th percentile threshold	1,152 (15%)	636 (14%)	5,808 (13%)

3.6 SELECTION OF MEASURES

The main criterion for selecting outcome measure was availability of the instrument that enabled separation of ADHD hyperactive-impulsive and inattention symptom domains. In each cohort, this type of instrument was available at child age 7.5 - 8 years. In ALSPAC, both maternal and teacher report were available (DAWBA), whereas in GenR and MoBa only a maternal reported instrument (CPRS-R and RS-DBD) was available. Correlations between ADHD total symptoms and hyperactive-impulsive and inattention symptom domains were more similar measured with DAWBA (r = 0.93) and RS-DBD (r = 0.90) compared to CPRS-R (r_{HYP} = 0.72; r_{INA} = 0.89). Moreover, in ALSPAC and GenR additional measures were included for ADHD subscale (SDQ, CBCL, TRF) as previous studies have reported different findings depending on whether child's ADHD symptoms were reported by mother or teacher, and which assessment instrument was used (Narad et al., 2015).

Given that paternal prenatal smoking, alcohol and caffeine use were assessed only during the partner's 2nd pregnancy trimester in each cohort (except in GenR where paternal caffeine consumption was not assessed and smoking and alcohol consumption were assessed 2 months prior their partner's pregnancy), exposures included in the analyses were based on the assessment during the 2nd pregnancy trimester.

Overall, correlations between maternal and paternal substance use were similar across the cohorts with a few exceptions. In ALSPAC and MoBa, the highest correlation of maternal prenatal substance use was with smoking and caffeine consumption (r_{ALSPAC} = 0.24; r_{MOBA} = 0.19) whereas in GenR it was between alcohol and caffeine consumption (r_{GENR} = 0.21). Furthermore, the highest correlation between maternal and paternal substance in ALSPAC and MoBa was in smoking (r_{ALSPAC} = 0.37; r_{MOBA} = 0.29) but in GenR it was in alcohol consumption (r_{GENR} = 0.39).

More detailed information about the measures and coding used in the analyses are described in the beginning of each study chapter.

3.7 CHAPTER SUMMARY

In this chapter, I have described the cohorts used in this thesis (ALSPAC, GenR and MoBa) and provided details about cohorts' participants, data availability, quality control of genome-wide data, and assessment of exposures and outcomes. Although availability of data varied between the cohorts, socio-demographic characteristics, and the assessment of exposures and outcome were comparable across the cohorts.

Chapter 4 MATERNAL AND CHILD GENETIC LIABILITY FOR SMOKING AND CAFFEINE CONSUMPTION AND CHILD MENTAL HEALTH: A PHENOME-WIDE ASSOCIATION STUDY IN THE ALSPAC COHORT

This chapter is based on the manuscript "Maternal and child genetic liability for smoking and caffeine consumption and child mental health: An intergenerational genetic risk score analysis in the ALSPAC cohort." The manuscript is published in Addiction journal https://doi.org/10.1111/add.15521

This study was a collaborative project undertaken by a group of PhD students and post-doctoral researchers. Given the ambitious nature of the project, we initially allocated tasks by exposures and outcomes. Polygenic risk scores were created by a post-doctoral researcher, Dr. Robyn Wootton, and a script for running the analyses was written by Dr. Kayleigh Easey. I extracted all the variables for maternal exposure and outcome phenotypes outside of pregnancy, as well as offspring externalising disorder phenotypes in childhood and adolescence and life events phenotype for all the subpopulations. Each of us prepared a dataset with their extracted variables and a final dataset was merged together. We cross-checked each other's work and the analyses for smoking were run by myself and checked by fellow PhD-student Laura Schellhas. I created all the figures and tables presented in this chapter. I drafted the discussion and interpretation of the results, in particular relative to smoking and offspring externalising disorders and sought comments from supervisors before revising for publication. Two manuscripts were written as a result of this work: the one presented in this chapter, on smoking and caffeine exposure, led by myself and Laura Schellhas and published as a joint first-authored paper, and a separate manuscript led by Dr Kayleigh Easey, on alcohol exposure, entitled "Characterization of alcohol polygenic risk scores in the context of mental health outcomes: Within-individual and intergenerational analyses in the Avon Longitudinal Study of Parents and Children" (Easey et al., 2021).

This chapter investigates associations between genetic risk scores predictive of smoking and caffeine consumption and mental health outcomes in mothers during and outside of pregnancy, and in offspring in childhood and adolescence, by using a targeted Phenome-Wide Association Study design.

4.1 INTRODUCTION

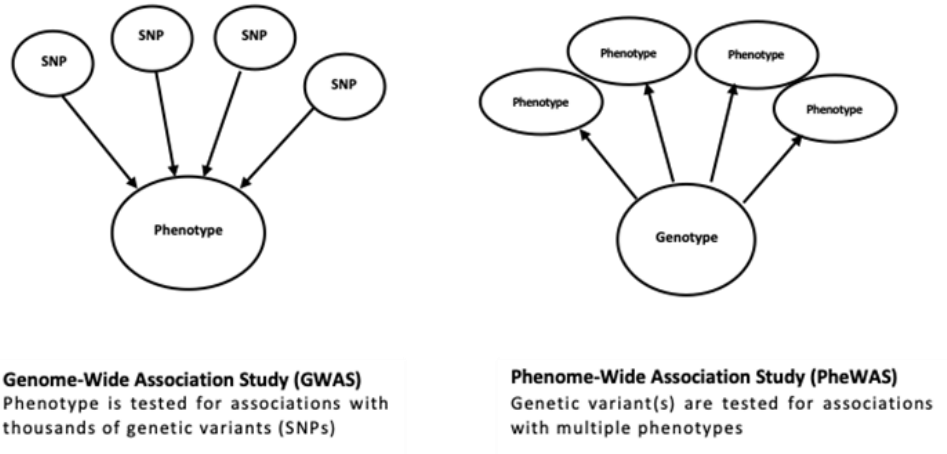
A large body of research has found that smoking and caffeine consumption are often comorbid, and associated with mental health problems and other substance use behaviours (Kendler et al., 2008; Lara, 2010; Treur et al., 2016).

However, by using observational methods it is difficult to ascertain whether these associations are causal, as they may be affected by unmeasured environmental confounders and/or explained by shared genetics, or due to evocative effects (reverse causation). Evocative effects reflect gene-environment correlations where parental behaviour is affected by children's genetically determined behaviour and there is evidence that the relationship between negative parenting behaviour and children's behavioural problems is bidirectional (Marceau et al., 2013). One approach to overcome biased associations because of unmeasured confounding or reverse causation is to use genetic variants as proxies for (environmental, modifiable) exposures (Davey Smith and Ebrahim, 2003). This approach is especially powerful in epidemiological studies where it is not feasible or ethical to conduct a randomised controlled trial, such as investigating effects of prenatal substance use on child health outcomes.

Large-scale genome-wide association studies (GWASs) have led to the discovery of thousands of genetic variants (single nucleotide polymorphisms, SNPs) associated with health outcomes and behavioural traits. These GWASs have revealed the polygenic nature of psychiatric disorders and traits (Maier et al., 2018; Visscher et al., 2012), although SNPs identified in GWASs explain only a small proportion of the trait variation, and may not truly identify causal genes (Tam et al., 2019; Visscher et al.,

2012). These SNPs can be aggregated into genetic risk scores and can help to predict genetic risk for a disease (Maier et al., 2018; Wray et al., 2014). The Phenome-Wide Association Study (PheWAS) method can be used to test associations between single genetic variants or genetic risk scores and a wide range of phenotypes (Figure 4.1).

Figure 4.1.Comparison of GWAS and PheWAS



The availability of large-scale data resources, such as from electronic health records, longitudinal studies or biobanks has made it possible to test associations between genetic variants and a broad range of phenotypes in this hypothesis-free manner (Leppert et al., 2020; Verma et al., 2019). The PheWAS approach is useful for replicating exposure-outcome associations found in GWASs, discovering novel associations, and detecting pleiotropic effects where the same genetic variants are associated with multiple traits (Pendergrass et al., 2013; Pendergrass et al., 2015).

For example, a PheWAS investigating alcohol and nicotine use in a sample of 26,394 women from different ethnicities replicated previously known genetic associations, such as the associations between smoking, lung cancer and asthma, as well as the associations between alcohol, education and income (Polimanti et al., 2016). However, this study also found indications for novel associations with metabolic and psychological traits

(Polimanti et al., 2016). The same study concluded that genetic variations underpinning alcohol and nicotine use have much broader effects than previously known, and that PheWAS is a powerful approach to discover these new potential pathways (Polimanti et al., 2016). Another PheWAS investigated associations between polygenic risk scores (PRSs) of five common psychiatric disorders (ADHD, autism, schizophrenia, major depression and bipolar disorder) and various socio-demographic, lifestyle, physical and mental health outcomes in UK Biobank. The authors concluded that besides major genetic overlap across the disorders, disorder-specific effects also exist. For instance, the PRS for ADHD was associated with a history of physical maltreatment, while the PRS for bipolar disorder was associated with higher educational attainment (Leppert et al., 2020).

Furthermore, PheWAS can be targeted, focusing on traits from specific domains such as psychopathology (Krapohl et al., 2016), or combined with other methods such as Mendelian Randomization (MR) to uncover which of the observed associations could be causal (Millard et al., 2015; Shen et al., 2020). Overall, PheWAS is an important emerging method to explore the genome and phenome together in a hypothesis-free manner to discover the genetic architecture of complex traits, and identify potential causal pathways.

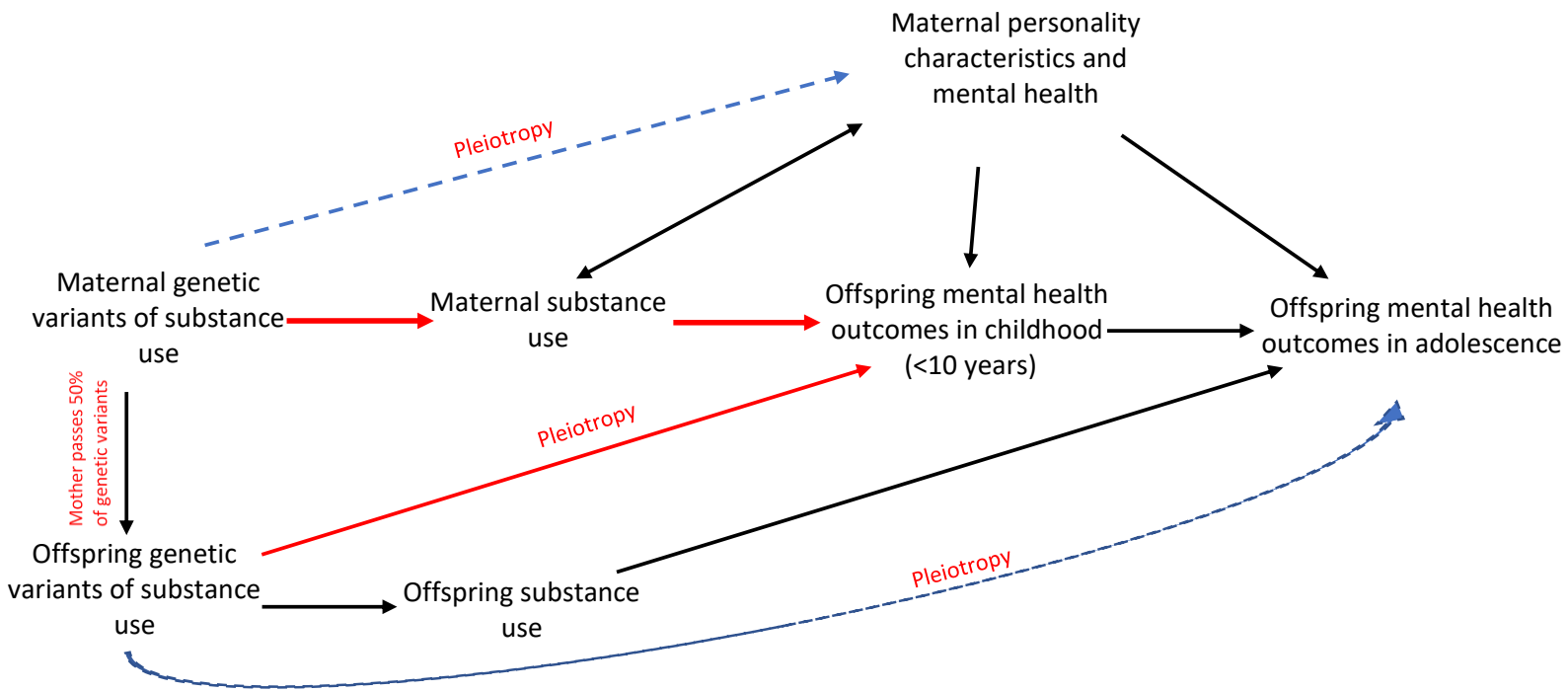
In this study, we used a targeted PheWAS approach to investigate whether maternal smoking and caffeine consumption are associated with mental health outcomes in offspring. The study aims were to: 1) validate that the PRS of smoking and caffeine consumption are associated with consumption of these substances in pregnancy and in adolescence. This is important as often GWAS has been conducted in non-pregnant adult populations and genetic variants identified in GWAS may not predict consumption behaviour during pregnancy (Lawlor et al., 2017); 2) investigate intergenerational effects by testing associations between maternal and offspring PRS and offspring outcomes in childhood before children are likely to consume these substances themselves (under age 10 years). This is important, because otherwise the offspring's own smoking or caffeine

consumption may confound associations; and lastly 3) disentangle potential causal effects from pleiotropic effects, by testing associations between maternal PRS and mothers own mental health outcomes during and outside of pregnancy as well as between offspring PRS on offspring mental health outcomes in adolescence. A visual representation of study aims is shown in Figure 4.2.

Comparing maternal PRS and offspring PRS analyses for offspring outcomes in childhood could give more indication whether some associations could be causal. As a child inherits 50% of their genetic variants from mother, a stronger maternal PRS and offspring outcome association could indicate effect through maternal environment (pre- and/or postnatal). Conversely, similar, associations between maternal PRS on maternal mental health outcomes during and outside of pregnancy, and offspring PRS on offspring mental health outcomes in adolescence, could give indications for potential pleiotropic effects. Conversely, similar associations across generations (childhood, adolescence, mothers during and outside of pregnancy) would reflect pleiotropic effects. Ideally maternal PRS analyses should be adjusted for offspring and paternal genetic data to avoid collider bias, but given the limited availability of paternal genetic data, often it is not possible. Therefore, we compared maternal and offspring PRS analyses on childhood outcomes to get more indication about potential causal effects.

It is important to note that the PheWAS approach alone cannot confirm whether observed associations are due to the intrauterine exposure to caffeine and smoking. Even if we observed that the maternal PRS associations are stronger than the offspring PRS associations, the former could reflect the effect of the maternal postnatal environment, such as maternal mental health status and parenting behaviour. In addition, maternal PRS associations may be a result of genetic nurturing, where genetic effects are mediated by the environment parents create for their children (Davies et al., 2019).

Figure 4.2.Overview of study aims using Directed acyclic graph (DAG)



Note: *Thick red arrows represent the main aim of the study: investigate intergenerational effects of maternal smoking and caffeine PRS on offspring mental health outcomes in childhood. To achieve this: 1) genetic variants of smoking and caffeine use were validated in pregnancy; 2) potential maternal environmental effects were disentangled from pleiotropic effects by testing associations between maternal and offspring PRS on offspring outcomes in childhood (<10 years). Childhood outcomes were selected under age 10 years as it is unlikely that in this age children are consuming these substances themselves. As child inherits 50% of genetic variants from mother, larger effect estimate with offspring PRS would reflect pleiotropic effect (red arrow); 3) to further disentangle causal effects from pleiotropic effects, associations were tested between maternal PRS on their own outcomes during and outside of pregnancy, as well as between offspring PRS on their own outcomes in adolescence (blue dashed arrows). Consistent associations across generations would reflect pleiotropic effects.*

4.2 METHODS

4.2.1 Study Population

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). More details about the ALSPAC cohort and genotype data can be found in Chapter 3 (see section 3.2 “The Avon Longitudinal Study of Parents and Children”).

4.2.2 Phenotype selection

The main focus of phenotype selection was mental health, but substance use and non-mental health phenotypes were also included based on the literature indicating high comorbidity with mental health (such as alcohol and cannabis use, personality traits, socioeconomic variables, body mass index, sleep, physical activity). Some variables were also included to check for confounding.

ALSPAC provides data at multiple timepoints for both mothers and offspring. We chose to include maternal phenotypes assessed during pregnancy (8, 18 and 32 weeks of gestation) and outside of pregnancy (pre- and post-pregnancy). Offspring data included phenotypes assessed in childhood (age 7-11 years) and adolescence (age 12-18 years). Maternal phenotypes assessed before child age 4 years were excluded as the transition to parenthood may affect mother’s mental health and mothers may be more likely to be pregnant again. For phenotypes that correlated highly, we only included the one with the larger sample size. We transformed continuous phenotypes that were not normally distributed into quantiles and if validated cut-off score was available, we derived binary phenotypes. We accounted for zero inflation by transforming continuous phenotypes with more than 20% of zero values into 3 categories (0, <median, >median).

We transformed caffeine phenotypes (coffee, tea, cola) based on their caffeine content. In ALSPAC, caffeine content for a cup of tea was 27mg, for a cup of coffee 57mg and for a can of cola (330ml) 20mg of caffeine (Farrow

et al., 1998). We computed total caffeine consumption per day by summing up each drink. We removed extreme outliers, such as consuming more than 28 cups of coffee and tea per day.

In total, we included 79 phenotypes for mothers during and outside of pregnancy and 71 phenotypes for offspring in childhood and adolescence. These are listed in Tables 4.1-4.4. The maximum sample size available in mothers during pregnancy was 7,269, outside of pregnancy 7,199, in offspring during childhood 6,156 and during adolescence 4,974.

We restricted the sample to singletons or one individual from a twin pair and to individuals of European ancestry. However, to avoid limiting sample size further, we did not restrict analyses to only mother-offspring pairs with complete genotype data. Participants who withdrew consent at any stage were removed from the analyses.

4.2.2.1 Maternal phenotypes during pregnancy

Maternal phenotypes assessed during pregnancy are shown in Table 4.1. All phenotypes were based on self-report using either questionnaires or single item questions.

Depression, anxiety, hypersensitivity to interpersonal rejection and number of life events were assessed using validated questionnaires.

Depression was assessed using Edinburgh Postnatal Depressions Scale (EPDS) developed by Cox and colleagues (Cox et al., 1987). Cut-off score ≥13 points was used as a threshold representing more severe depression symptoms (Cox et al., 1996).

Anxiety was assessed with the anxiety sub-scale of the Crown-Crisp Experiential Index (CCEI). Cut-off score 85th percentile has been used in previous studies representing more severe anxiety symptoms (Capron et al., 2015; Heron et al., 2004).

Hypersensitivity to interpersonal rejection was measured with Interpersonal Sensitivity Measure (IPSM) (Boyce and Parker, 1989) which has been found to be correlated with neuroticism personality trait (Boyce et al., 1990). The IPSM has 5 subscales: inter-personal awareness, need for approval, separation anxiety, timidity and fragile inner self. Total score of all the subscales was included in the analyses.

Life events were measured with the Life Events Inventory which includes 42 life events (Barnett et al., 1983).

Table 4.1. Maternal phenotypes during pregnancy

Mental health	Timepoint	Substance use	Timepoint	Non-mental health phenotypes	Timepoint
Binary phenotypes					
Depression symptoms	18 weeks	Smoked first three months in pregnancy	18 weeks	Physical activity	32 weeks
Depression symptoms	32 weeks	Ever smoked during pregnancy	8 weeks	Mother vomited first three months of pregnancy	18 weeks
Hypersensitivity to interpersonal rejection	18 weeks	Stopped smoking	8 weeks		
		Cut down smoking	8 weeks		
Anxiety symptoms	18 weeks	Doing hard drugs	18 weeks		
		Cannabis use first three months in pregnancy	8 weeks		
		Consumed more caffeine	8 weeks		
		Never been drinking caffeine	8 weeks		
		Did not change caffeine consumption	8 weeks		
		Reduced caffeine consumption	8 weeks		
		Never drank tea	8 weeks		
		Reduced tea consumption	8 weeks		
		Craved or had more tea	8 weeks		
		Never drank coffee	8 weeks		
		Stopped drinking coffee	8 weeks		
		Reduced coffee consumption	8 weeks		
		Craved or had more coffee	8 weeks		
		Never drank cola	8 weeks		
		Stopped drinking cola	8 weeks		
		Reduced cola consumption	8 weeks		
		Craved or had more cola	8 weeks		
		Cut down cola consumption	8 weeks		

Continuous phenotypes				
	Binge drinking	18 weeks	Number of life events	18 weeks
	Binge drinking	32 weeks	Reactions to becoming a parent	18 weeks
	Alcohol consumption per week	32 weeks	Social class	32 weeks
	Total caffeine mg/day	18 weeks	Highest education	32 weeks
	Tea mg/day	18 weeks	Activity level compared with other pregnant women	32 weeks
	Coffee mg/day	18 weeks	Image-perception during pregnancy	18 weeks
	Cola mg/day	18 weeks	Image-perception change from before to during pregnancy	18 weeks
	Total caffeine mg/day	32 weeks		
	Tea mg/day	32 weeks		
	Coffee mg/day	32 weeks		
	Cola mg/day	32 weeks		

4.2.2.2 Maternal phenotypes outside of pregnancy

Maternal phenotypes assessed outside of pregnancy (pre- and post-pregnancy) are shown in Table 4.2. All phenotypes were assessed using self-report. Validated questionnaires were available measuring depression, anxiety, life events, personality traits and alcohol use based on risk levels.

Depression, anxiety and number of life events were measured with the same questionnaire as during pregnancy. Although EPDS was originally developed to measure post-natal depression, this instrument has also been validated for measuring depression outside of pregnancy (Cox et al., 1996; Thorpe et al., 1993).

Personality traits were measured using the Karolinska Scale of Personality (KSP). This instrument was developed to measure personality traits relevant for assessing psychopathology in psychiatry (Gustavsson et al., 1997). The KSP measures 15 personality traits which are assessed in subscales: somatic anxiety, psychic anxiety, muscular tension, psychasthenia, inhibition of aggression, irritability, guilt, socialization, social desirability, monotony avoidance, impulsivity, verbal aggression, indirect aggression, suspicion and detachment.

Although previous studies have found that the KSP is comparable with other personality questionnaires, such as the Eysenck Personality Questionnaire and "Big Five" personality factors from the International Personality Item Pool, it has been also found that individual items in some subscales overlap with items included in other subscales (Gustavsson et al., 2000; Ortet et al., 2002). Considering this, personality traits included in this study were based on a previous study in ALSPAC where latent variable analysis was performed to construct the traits distinct from other domains (Pearson et al., 2018). These five traits included in the study were: monotony avoidance, impulsivity, verbal anger, suspicion and detachment. In addition, the majority of the original KSP subscales are

associated with neuroticism and given that the neuroticism phenotype was already included during pregnancy (hypersensitivity to interpersonal rejection), no additional KSP personality traits associated with neuroticism were included.

Table 4.2. Maternal phenotypes outside of pregnancy

Mental health	Timepoint	Substance use	Timepoint	Non-mental health phenotypes	Timepoint
Binary phenotypes					
Anxiety score	11 years	Ever been a smoker	18 weeks	Physical activity	18 years
Depression score	11 years	Mother drank before pregnancy	18 weeks		
Ever had bulimia	12 weeks				
Ever had alcoholism	12 weeks				
Ever had drug addiction	12 weeks				
Ever had schizophrenia	12 weeks				
Ever had anorexia nervosa	12 weeks				
Ever had severe depression	12 weeks				
Ever had other psychiatric problem	12 weeks				
Image perception before pregnancy	18 weeks				
Continuous phenotypes					
Image perception before pregnancy	18 weeks	Number of cigarettes smoked before pregnancy	18 weeks	Number of life events	11 years
		Number of cigarettes smoked last 2 weeks	8 years	Impulsivity trait	9 years
		Total caffeine intake mg/day	8 years	Monotony avoidance trait	9 years
		Caffeine intake from coffee mg/day	8 years	Anger trait	9 years
		Caffeine intake from tea mg/day	8 years	Suspicion trait	9 years
		Caffeine intake from cola mg/day	8 years	Detachment trait	9 years
		Alcohol consumption daily/units	8 years	Social class	4 years
		Binge drinking	5 years	Highest education	5 years
		Alcohol consumption daily/units	4 years	BMI before pregnancy	12 weeks
		AUDIT score	18 years		

4.2.2.3 Offspring phenotypes in childhood

Offspring phenotypes assessed in childhood are shown in Table 4.3. Included phenotypes were measured at child age 7 to 10 years. Most of the childhood phenotypes were based on maternal report. Only IQ was assessed during the clinic visit and based on the Wechsler Intelligence Scale (The WISC-III) (Wechsler et al., 1992). The WISC-III consists of 10 subtests: 5 of these are assessing verbal abilities and other 5 non-verbal (performance) abilities.

Validated questionnaires were available for measuring externalising disorder and internalising disorder symptoms. ADHD, conduct disorder and emotional problems symptoms were assessed with the SDQ instrument. Oppositional-defiant disorder (ODD) and anxiety disorder symptoms were assessed with the DAWBA instrument. Specific phobia phenotype was derived based on DAWBA bands. Both instruments have been described in more detail in Chapter 3 (see section 3.2.2. "ADHD assessment in ALSPAC"). Depression symptoms were additionally measured with the Short Mood and Feelings Questionnaire (SMFQ) (Angold et al., 1995; Messer et al., 1995). The Life Events Inventory was used to measure number of life events a child had experienced.

Autism diagnosis was derived combining DSM criteria from various measures reflecting social, communication and repetitive behaviours up to age 9 years (Steer et al., 2010).

Handedness was included as a negative control phenotype, as no association was expected between smoking and caffeine PRS and handedness.

Table 4.3. Offspring phenotypes in childhood

Mental health	Age	**Substance use**	**Age**	**Non-mental health phenotypes**	**Age**
Binary phenotypes					
Specific phobia diagnosis	9.5 years	Daily tea consumption	8 years	Problems with sleep initiation	6.7 years
Autism diagnosis	9 years	Daily coffee consumption	8 years	Problems with sleep maintenance	6.7 years
Continuous phenotypes					
ADHD symptoms	6.7 years	Total caffeine intake mg/day	8 years	Sleep duration in hours	6.7 years
Conduct disorder symptoms	6.7 years			Number of life events	6.7 years
Oppositional-defiant disorder symptoms	7.6 years			IQ	8 years
Depression symptoms	9.5 years			BMI	7 years
Emotional problems symptoms	6.8 years			Handedness (negative control phenotype)	11 years
Anxiety symptoms	7.5 years				
Total behavioural difficulties	6.7 years				

4.2.2.4 Offspring phenotypes in adolescence

Offspring phenotypes assessed in adolescence are shown in Table 4.4. Offspring phenotypes in adolescence were based on self-report and maternal reports and measured at age 12 to 18 years.

Maternal report was used for externalising and internalising disorder phenotypes assessed with the SDQ, DAWBA and SMFQ scales. Post-traumatic stress-disorder diagnosis was derived using DAWBA bands.

Maternal report was also used for assessing adolescent caffeine consumption. Self-report was used for depression, anxiety and phobia symptoms assessed with the revised Clinical Interview Schedule (CIS-R) (Lewis et al., 1992). The depression phenotype used in this study was a sum of 5 depression symptom scores. Anxiety and phobia phenotypes were based on total symptom scores.

Psychosis interview was used to measure negative and positive symptoms of psychosis. Additionally, measures of psychosis-like symptoms (PLIKS) were used to assess negative symptoms of psychosis which some are based on Diagnostic Interview Schedule version IV (DISC-IV) (Zammit et al., 2008). Self-harming behaviour phenotype was derived from combining items from multiple questionnaires (Easey, Mars, et al., 2019).

Personality traits were assessed with the International Personality Item Pool (IPIP) (Goldberg, 1999) which investigates the “Big Five” personalities: extraversion, neuroticism, agreeableness, conscientiousness and openness.

Adolescents had to answer about their own smoking and alcohol consumption and the Alcohol Use Disorders Identification Test (AUDIT) was used to derive total score of problematic alcohol consumption and risk levels of alcohol consumption (Liskola et al., 2018; Saunders et al., 1993). These risk levels have been grouped to “low risk”, “hazardous”, “harmful” and “high risk”.

Table 4.4. Offspring phenotypes in adolescence

Mental health	Rater	Age	Substance use	Rater	Age	Non-mental health phenotypes	Rater	Age
Binary phenotypes								
Post-traumatic stress disorder	self	15 years	Ever tried cannabis	self	16.5 years	GCSE grades A-C	self	18 years
Self-harming behaviour	self	15 years	Smoked a cigarette	self	14 years	GCSE grades D-G	self	18 years
Ever treated for eating disorder	self	13 years	Number of cigarettes smoked	self	14 years			
Ever treated for eating disorder	self	16 years	Smoked a whole cigarette	self	18 years			
Continuous phenotypes								
ADHD symptoms	maternal	16.6 years	AUDIT score (frequency of alcohol consumption)	self	17 years	Sleep duration	self	15.5 years
Conduct disorder symptoms	maternal	16.6 years	AUDIT (risk levels of alcohol consumption)	self	17 years	Number of life-events	self	16.5 years
Oppositional-defiant disorder symptoms	maternal	15.5 years	Binge drinking	self	17 years	Extraversion personality trait	self	13 years
Depression symptoms (CIS-R)	self	18 years	Number of drinks needed to feel tipsy	self	17 years	Agreeableness personality trait	self	13 years
Depression symptoms (SMFQ)	maternal	17 years	Number of alcoholic drinks consumption in a typical day	self	18 years	Conscientiousness personality trait	self	13 years
Depression symptoms (SMFQ)	maternal	14 years	AUDIT total score	self	18 years	Emotional stability (neuroticism) personality trait	self	13 years
Emotional problems symptoms	maternal	16.5 years	Number of times had whole drink	self	12 years	Intellect (openness) personality trait	self	13 years
Anxiety symptoms	self	17 years	Number of drinks had to feel different	self	12 years	Sleep maintenance	self	15 years
Phobia symptoms	self	17 years	Number of times had 3+ drinks in one day	self	12 years	Sleep initiation	self	15 years
Total behavioural difficulties	maternal	16.5 years	Age when first smoked a cigarette	self	14 years	Frequency of doing exercise	self	14 years
Psychosis positive symptoms	self	12 years	Age when first smoked whole cigarette	self	18 years	BMI	self	17 years

Psychosis negative symptoms	self	16 years	Number of cigarettes smoked in lifetime	self	18 years	IQ	self	15.5 years
Psychosis positive symptoms	self	18 years	Frequency of smoking cannabis	self	16.5 years			
			Total caffeine intake mg/day	maternal	13 years			
			Caffeine intake from tea mg/day	maternal	13 years			
			Caffeine intake from coffee mg/day	maternal	13 years			
			Caffeine intake from cola mg/day	maternal	13 years			

Note: GCSE - General Certificate of Secondary Education

4.2.3 Polygenic risk scores (PRSs)

We calculated PRSs for smoking and caffeine for mothers and offspring using effect estimates based on summary data from recent GWAS of tobacco (Liu et al., 2019) and coffee consumption (Cornelis et al., 2015). We used PLINK v1.90 (Purcell et al., 2007) to compute weighted average scores and standardized these using z-score transformation.

4.2.3.1 Smoking PRS

The GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN, N=1.2 million) identified 378 SNPs associated with smoking initiation that were conditionally independent at the genome-wide significance level of 5×10^{-8}. Smoking initiation was defined as being an 'ever' vs. 'never smoker' where an 'ever smoker' had to have either smoked 100 cigarettes in their lifetime and/or smoked regularly every day for at least a month (Liu et al., 2019). Of the 378 genome-wide significant SNPs, 356 were available in ALSPAC.

4.2.3.2 Caffeine PRS

The Coffee and Caffeine Genetics Consortium (N=91,462) found 8 SNPs to be independently associated with cups of coffee consumed per day at the genome-wide level of significance (Cornelis et al., 2015), which were all available in ALSPAC. Although the GWAS was conducted only on coffee consumption, these SNPs have also been found to be associated with overall caffeine use from other caffeinated beverages, such as tea and cola but not from cola alone (McMahon et al., 2014; Treur et al., 2016).

4.2.4 Statistical analysis

We performed all analyses using Stata v15 (StataCorp, 2017). We conducted linear and logistic regression analyses to test associations of the smoking and caffeine PRS with 1) exposure phenotypes in mothers during and outside of pregnancy and offspring (caffeine consumption in childhood and adolescence; smoking in adolescence); 2) childhood phenotypes (under

age 10 years) for investigating intergenerational effects; 3) phenotypes in mothers during and outside of pregnancy and adolescence in offspring to disentangle potential causal effects from pleiotropic effects.

We adjusted analyses for age, offspring gender and the first 10 ancestry-informative principal components. Principal components analysis was used to adjust for underlying population structure due to the allele frequency differences in different ancestries (Price et al., 2006). Failure to take into account ancestry differences can cause biased associations even in more homogenous populations (Seldin et al., 2006).

Due to the large number of tests, we accounted for multiple testing by using Bonferroni correction and Monte Carlo permutation testing. Since Bonferroni correction is over-conservative and does not take into account correlations between the phenotypes, we also included permutation testing with 1000 repetitions. Both methods have been widely used in genetic studies where false positive findings because of large number of tests is a persistent problem (Goeman and Solari, 2014). The Bonferroni correction p-value is obtained by dividing $p<0.05$ by the number of independent tests performed. Alternatively, permutation testing randomly allocates the exposure values between individuals in the sample and reanalyses the resulting dataset. In a permutation test, the resulting p-value is the number of times the test statistic observed in the randomly shuffled data is as, or more extreme than, the test statistic observed in the original dataset divided by the number of permutations. Given the correlation between the phenotypes, we used permutation testing as the main analysis for multiple correction, but considered the strongest evidence for associations that also survived Bonferroni correction – the latter being more stringent and therefore more conservative.

4.2.4.1 Sensitivity analyses

Given the complex nature of smoking behaviour, it is also important to consider smoking heaviness and cessation while investigating the effects of prenatal smoking on offspring health outcomes. Therefore, we used the genetic instrument of lifetime smoking to capture effects of smoking

behaviours beyond initiation. The lifetime smoking instrument is a combined measure of four smoking phenotypes: smoking status (current, former, never), smoking duration, smoking heaviness (number of cigarettes smoked per day) and smoking cessation which is derived from the entire population comprising both smokers and non-smokers and therefore is more suitable for use in unstratified samples (Wootton et al., 2020). The GWAS of lifetime smoking based on UK Biobank (N=462,690) identified 126 independent SNPs at the genome-wide significant level of which 123 were available in ALSPAC. Consistent results between the lifetime smoking and smoking initiation instruments would give more confidence that the associations were not false positives but rather the result of smoking behaviour beyond initiation.

4.3 RESULTS

4.3.1 Aim 1: Validation of smoking and caffeine PRSs

Associations between smoking initiation and lifetime smoking PRSs on exposure phenotypes in mothers and adolescence are shown in Tables 4.5 and Appendix 4.1.

Both, maternal and offspring smoking initiation and lifetime smoking PRS predicted smoking in mothers and offspring in adolescence. In pregnancy, maternal smoking initiation PRS was not associated with smoking cessation phenotype but association with smoking cessation was observed with the maternal lifetime smoking PRS (see Appendix 4.1). This is expected as lifetime smoking PRS captures also smoking cessation behaviour. The maternal PRSs for smoking initiation and lifetime smoking explained 1-5% of variance in smoking phenotypes during and outside of pregnancy.

In adolescence, offspring smoking initiation PRS was not associated with a cigarette smoked at age 14, while the offspring lifetime smoking PRS was not associated with number of cigarettes smoked in lifetime reported at age 14 and 18. This could be explained by the small sample size of these phenotypes (N = 1,058 to 1,144).

The offspring PRSs for smoking initiation and lifetime smoking explained 0.2-3% of variance in smoking phenotypes in adolescence.

Table 4.5. Associations between maternal and offspring smoking initiation PRSs and smoking phenotypes in mothers and adolescence

Phenotype	Effect estimate	Effect size*	95% CI	P-value	Sample size	R^2
Mothers during of pregnancy						
Tobacco smoked in 1st three months of pregnancy	OR	1.35	1.226, 1.440	$3.0x10^{-7}$	7,237	0.05
Mother cut down smoking	OR	1.33	1.248, 1.423	$5.89x10^{-7}$	7,269	0.03
Mother stopped smoking during pregnancy	OR	0.98	0.876, 1.105	0.771	1,863	0.01
Mothers outside of pregnancy						
Mother has ever smoked	OR	1.40	1.325, 1.476	$1.24x10^{-8}$	7,194	0.03
Number of cigarettes smoked before pregnancy	Beta	0.15	0.078, 0.220	$3.81x10^{-5}$	3,426	0.05
Offspring: Adolescents						
Smoked at age 14 years	OR	1.18	1.089, 1.279	$6.50x10^{-4}$	4,145	0.03
Smoked more than 20 cigarettes at age 14	OR	1.19	1.027, 1.382	0.024	1,058	0.03
Age 1st smoked a cigarette (asked at age 14)	Beta	0.001	-0.04, 0.042	0.953	1,064	0.01
Ever smoked a whole cigarette at age 18	OR	1.26	1.147, 1.374	$1.09x10^{-4}$	2,402	0.02
Number of cigarettes smoked in lifetime at age 18	Beta	0.19	0.098, 0.278	$4.24x10^{-5}$	1,144	0.01

Note: Reflects the average change in the outcome that is associated with a one standard deviation increase in the PRS. For binary outcomes, this will be the odds ratio (OR) (e.g., mother's odds of ever smoking are 1.4 times compared to not smoking), for continuous outcomes it represents the average unit change (e.g., 0.15 cigarettes smoked); 95% CI – 95% confidence intervals; R^2 – variance explained

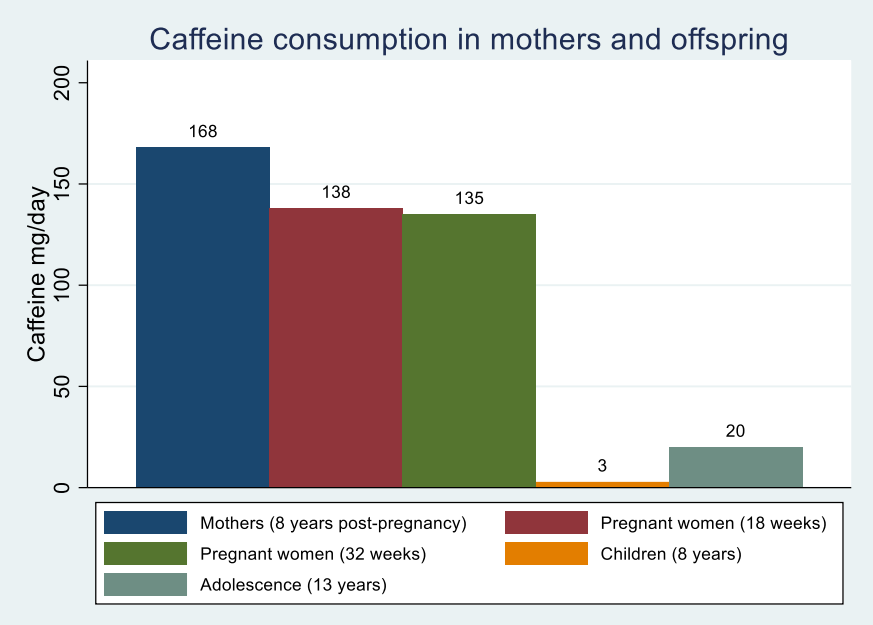
Results testing the associations between caffeine PRS on exposure phenotypes in mothers and offspring are shown in Table 4.6.

Maternal caffeine PRS predicted total caffeine consumption and separately coffee and tea consumption but not cola consumption in mothers during and outside of pregnancy. The maternal caffeine PRS explained 0.2-1% of variance in caffeine phenotypes during pregnancy and outside of pregnancy.

Offspring caffeine PRS was not associated with total caffeine consumption and neither separately with coffee, tea or cola consumption in childhood and adolescence. This could be explained by low levels of caffeine consumption in childhood and adolescence. The offspring caffeine PRS explained 0.1-0.4% of variance in caffeine phenotypes in childhood and 0.4-2% variance in caffeine phenotypes in adolescence.

Overview of median daily caffeine consumption across generations is shown in Figure 4.3.

Figure 4.3. Median caffeine consumption in mg/day in mothers and offspring



Furthermore, mothers who reported smoking during pregnancy drank more caffeine ($Median_{18wks}$ = 190mg/day; Interquartile range (IQR) = 116-282mg/day; $Median_{32wks}$ = 189mg/day; IQR = 108-279mg/day) compared with mothers who did not smoke during pregnancy ($Median_{18wks}$= 127mg/day; IQR = 73-191mg/day; $Median_{32wks}$= 114mg/day; IQR = 57-189mg/day). Similarly, mothers who reported smoking 8 years post-pregnancy consumed more caffeine (Median = 225mg/day; IQR = 135-339mg/day) compared with mothers who did not smoke (Median = 168mg/day; IQR = 108-249mg/day).

Table 4.6. Associations between maternal and offspring caffeine PRSs and daily caffeine intake in mothers and offspring

	Daily caffeine intake phenotype	Effect size* (beta)	95% CI	P-value	Sample size	R^2
Mothers during pregnancy – 18 weeks gestation	Total (coffee, tea and cola)	5.85	3.092, 8.614	$3.28x10^{-5}$	7,220	0.004
	Coffee	0.02	0.005, 0.042	0.011	7,198	0.002
	Tea	0.02	0.006, 0.041	0.007	7,189	0.002
	Cola	-0.001	-0.016, 0.014	0.890	7,185	0.002
Mothers during pregnancy – 32 weeks gestation	Total (coffee, tea and cola)	6.32	3.741, 8.892	$1.56x10^{-6}$	6,767	0.01
	Coffee	0.03	0.007, 0.043	0.006	6,596	0.002
	Tea	3.42	1.795, 5.036	$3.65x10^{-5}$	6,608	0.004
	Cola	-0.01	-0.028, 0.008	0.278	6,500	0.002
Mothers outside of pregnancy	Total (coffee, tea and cola)	9.89	6.337, 13.435	$4.97x10^{-8}$	4,783	0.01
	Coffee	0.03	0.008, 0.055	0.009	4,655	0.003
	Tea	0.07	0.033, 0.099	$1.01x10^{-4}$	4,632	0.01
	Cola	0.01	-0.012, 0.034	0.332	4,670	0.002
Offspring: Childhood – age 8 years	Total (coffee, tea and cola)	0.01	-0.012, 0.032	0.377	4,589	0.002
	Coffee	0.01	-0.063,0.077	0.845	254	0.004
	Tea	0.18	-1.517, 1.875	0.836	1,475	0.001
	Cola	0.003	-0.021, 0.026	0.829	4,551	0.002
Offspring: Adolescence – age 13 years	Total (coffee, tea and cola)	0.01	-0.030, 0.046	0.670	3,405	0.004
	Coffee	0.03	-0.023, 0.081	0.271	467	0.02
	Tea	0.89	-0.353, 2.125	0.161	1,933	0.004
	Cola	-0.02	-0.052, 0.022	0.424	2,411	0.01

Note: Reflects the average change in the outcome that is associated with a one standard deviation increase in the PRS. In mothers outside of pregnancy, a one standard deviation increase in caffeine PRS is association with a 9.9mg increase in total caffeine consumption; 95 % CI – 95% confidence intervals; R^2 – variance explained

4.3.2 Aim 2: Maternal and offspring PRS associations on offspring phenotypes in childhood

4.3.2.1 Smoking Initiation PRS

Maternal smoking initiation PRS: Several associations were observed between the maternal smoking initiation PRS and offspring phenotypes in childhood. These results are shown in Figure 4.4.

The associations observed with the childhood mental health phenotypes were with reduced anxiety symptoms (β_{8years} = -0.03, 95% CI-0.053, -0.012, P_{perm} = 0.002) and increased conduct disorder symptoms (β_{7years} = 0.02, 95% CI 0.004, 0.044, P_{perm} = 0.021). The strongest associations observed with the non-mental health phenotypes were with lower IQ (β_{8years} = -0.59, 95% CI -1.049, -0.134, P_{perm} = 0.016) and higher BMI (β_{7years} = 0.08, 95% CI 0.018, 0.135, P_{perm} =0.001). Among the substance use phenotypes, an association was observed with higher overall caffeine consumption (mg/day; β_{8years} = 0.05, 95% CI 0.021, 0.068, P_{perm} = <0.001). Additionally, an association with higher likelihood of being left-handed ($OR_{11years}$ = 1.11, 95% CI 1.012, 1.225, P_{perm} = 0.012) was observed, despite this being included as a negative control phenotype.

After applying Bonferroni correction (P<0.003), we found the strongest evidence for offspring anxiety symptoms and caffeine consumption phenotypes.

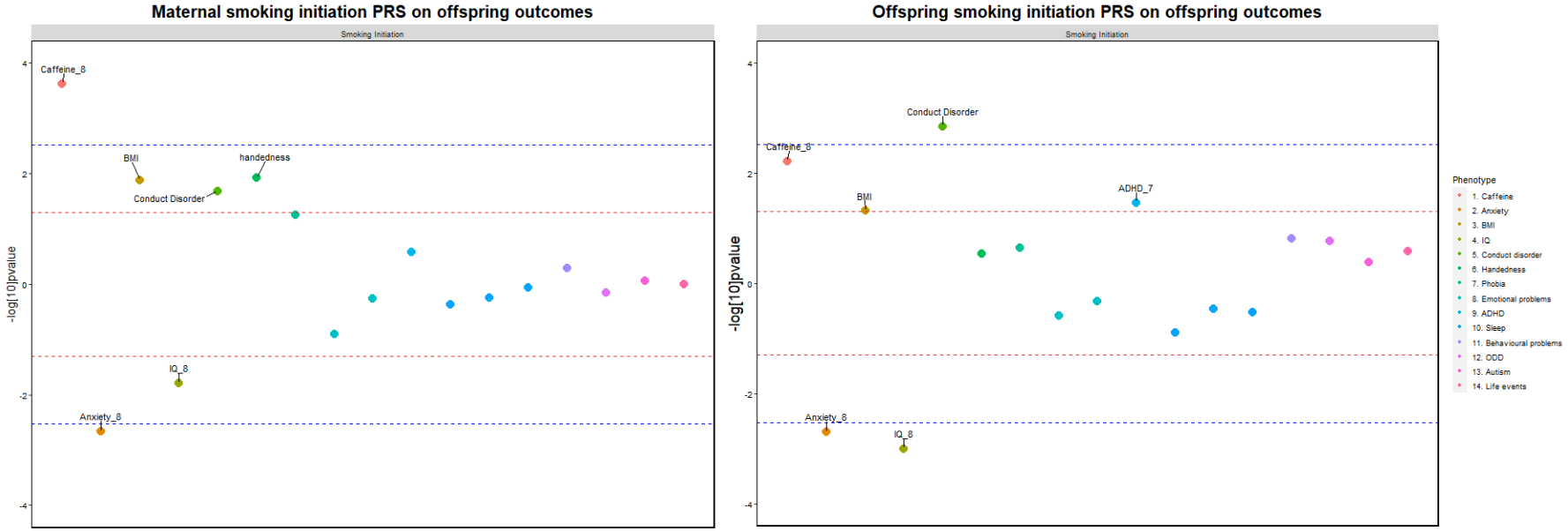
Offspring smoking initiation PRS: Results for the offspring smoking initiation PRS on childhood outcomes are shown in Figure 4.4.

Similarly to the maternal smoking initiation PRS analyses, associations were observed with reduced anxiety symptoms (β_{8years} = -0.03, 95% CI -0.051,-0.010, P_{perm} = 0.002) and increased conduct disorder symptoms (β_{7years} = 0.03, 95% CI 0.012, 0.049, P_{perm} = 0.001). Additionally, an association was observed with ADHD symptoms (β_{7years} = 0.03, 95% CI 0.003, 0.058, P_{perm} =

0.034). Offspring smoking initiation PRS showed similar associations with the substance use and non-mental health phenotypes as maternal smoking initiation PRS: lower IQ (β_{8years} = -0.74, 95% CI-1.183, -0.287, P_{perm} = <0.001), higher BMI (β_{7years} = 0.05, 95% CI-0.0003, 0.101, P_{perm}=0.048), and higher caffeine consumption (mg/day; β_{8years} = 0.03, 95% CI 0.010, 0.055, P_{perm} = 0.006). However, an association with left-handedness was not observed for the offspring smoking initiation PRS ($OR_{11years}$ = 1.05, 95% CI 0.954, 1.145, P_{perm} = 0.291). After applying Bonferroni correction (P<0.003), we found the strongest evidence with IQ and conduct disorder symptoms phenotypes.

Full results with maternal and offspring smoking initiation PRS on childhood outcomes are shown in Table 4.7.

Figure 4.4. Comparison of associations between maternal and offspring smoking initiation PRSs on offspring outcomes in childhood



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.003 after Bonferroni correction

Table 4.7. Associations between maternal and offspring smoking initiation PRSs and offspring phenotypes in childhood

		Maternal smoking initiation PRS analyses						Offspring smoking initiation PRS analyses					
		Regression analyses			Permutation testing			Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Total caffeine	Beta	0.05	0.021, 0.068	0.0002	<0.001, 0.004	<0.001	4,067	0.03	0.010, 0.055	0.005	0.002, 0.013	0.006	4,589
Anxiety	Beta	-0.03	-0.053, -0.012	0.002	<0.001, 0.007	0.002	4,993	-0.03	-0.051, -0.010	0.003	<0.001, 0.007	0.002	5,355
BMI	Beta	0.08	0.018, 0.135	0.010	0.007, 0.022	0.013	5,032	0.05	<0.001, 0.101	0.051	0.036, 0.063	0.048	5,799
IQ	Beta	-0.59	-1.049, -0.134	0.011	0.009, 0.026	0.016	4,675	-0.74	-1.183, -0.287	0.001	<0.001, 0.004	<0.001	5,295
Conduct disorder	Beta	0.02	0.004, 0.044	0.019	0.013, 0.032	0.021	5,012	0.03	0.012, 0.049	0.001	<0.001, 0.006	0.001	5,326
Handedness	OR	1.11	1.012, 1.225	0.030	0.006, 0.021	0.012	4,849	1.05	0.954, 1.145	0.315	0.263, 0.320	0.291	5,403
Specific phobia	OR	1.32	0.964, 1.813	0.078	0.042, 0.071	0.055	5,100	1.18	0.881, 1.587	0.241	0.199, 0.252	0.225	5,470
Emotional problems	Beta	-0.02	-0.037, 0.004	0.117	0.106, 0.148	0.126	5,139	-0.01	-0.031, 0.009	0.267	0.236, 0.291	0.263	5,459
ADHD	Beta	0.02	-0.013, 0.045	0.277	0.232, 0.287	0.259	4,916	0.03	0.003, 0.058	0.030	0.024, 0.047	0.034	5,219
Sleep duration	Beta	-0.01	-0.033, 0.014	0.426	0.392, 0.454	0.423	5,127	-0.02	-0.042, 0.004	0.106	0.107, 0.149	0.127	5,443
Behavioural difficulties	Beta	0.01	-0.021, 0.041	0.522	0.482, 0.544	0.513	5,133	0.02	-0.008, 0.051	0.152	0.130, 0.176	0.152	5,452
Depression	Beta	-0.01	-0.027, 0.015	0.557	0.524, 0.586	0.555	4,885	-0.01	-0.027, 0.012	0.466	0.442, 0.504	0.473	5,434
Sleep maintenance	OR	0.98	0.919, 1.051	0.589	0.534, 0.596	0.565	5,127	0.97	0.913, 1.038	0.383	0.313, 0.372	0.342	5,448
ODD	Beta	-0.004	-0.024, 0.016	0.700	0.683, 0.740	0.712	4,943	0.02	-0.005, 0.034	0.148	0.146, 0.194	0.169	5,319
Autism	OR	1.03	0.722, 1.460	0.874	0.860, 0.901	0.882	5,975	1.15	0.803, 1.654	0.411	0.380, 0.442	0.411	6,156
Sleep initiation	OR	0.99	0.934, 1.061	0.874	0.827, 0.873	0.851	5,150	0.97	0.913, 1.032	0.309	0.269, 0.326	0.297	5,476
Life events	Beta	<0.001	-0.018, 0.019	0.996	0.991, 0.999	0.997	5,167	0.01	-0.008, 0.028	0.271	0.237, 0.292	0.264	5,493

Note: OR-odds ratio; 95% CI – 95% confidence intervals

4.3.2.2 Caffeine PRS

Maternal caffeine PRS: Results for the maternal caffeine PRS and childhood outcomes analyses are shown in Figure 4.5.

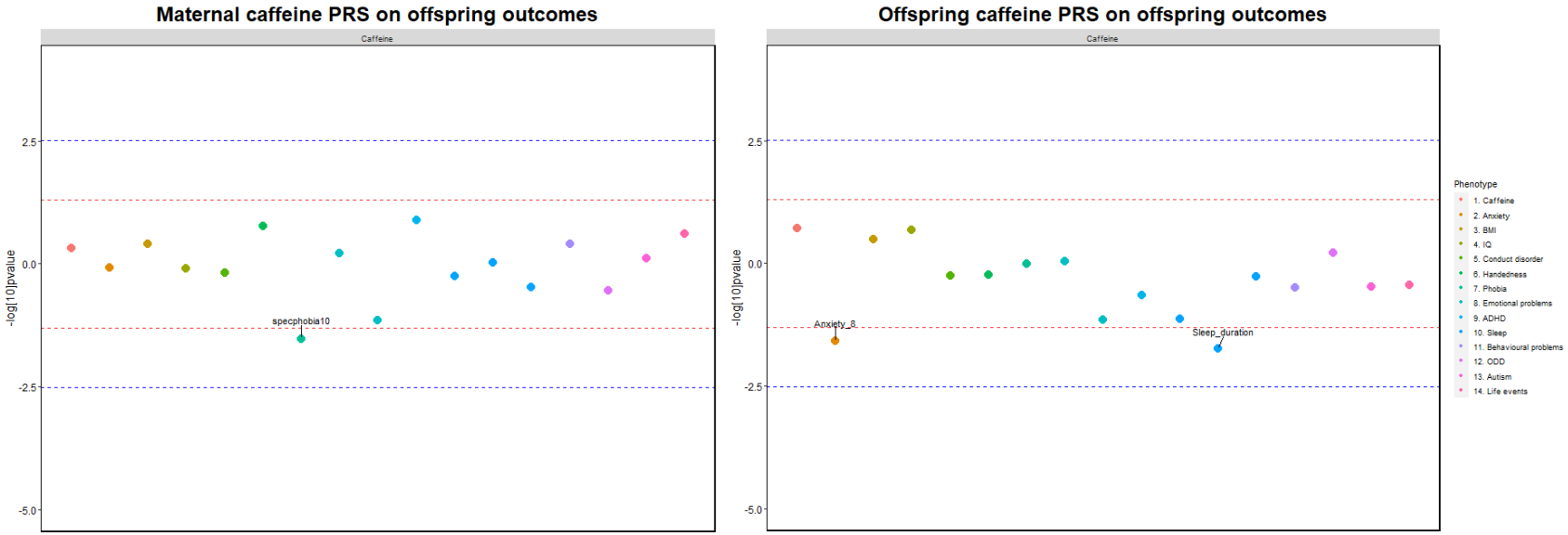
Maternal caffeine PRS was associated only with one childhood phenotype, which was decreased risk for specific phobias ($OR_{10years}$ = 0.72, 95% CI 0.519, 1.012, P_{perm}= 0.028). However, this association did not survive Bonferroni correction (P<0.003).

Offspring caffeine PRS: Results for the offspring caffeine PRS analyses and childhood outcomes are shown in Figure 4.5. Given that offspring caffeine PRS was not associated with caffeine consumption in childhood, we were able to use these results as a test for pleiotropy.

Compared to the findings with maternal caffeine PRS, the offspring caffeine PRS analyses did not show evidence for association with the specific phobia phenotype ($OR_{10years}$ = 1.00, 95% CI 0.723, 1.381, P_{perm}= 0.998). However, offspring caffeine PRS was associated with fewer anxiety symptoms (β_{8years} = -0.02, 95% CI -0.042, -0.002, P_{perm} = 0.026) and fewer hours of sleep (β_{7years} = -0.03, 95% CI -0.048, -0.004, P_{perm} = 0.018). However, the evidence for these associations was weak as none survived Bonferroni correction (P<0.003).

Full results for the maternal and offspring caffeine PRS and childhood outcomes analyses are presented in Table 4.8.

Figure 4.5. Comparison of associations between maternal and offspring caffeine PRSs on offspring outcomes in childhood



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.003 after Bonferroni correction

Table 4.8. Associations between maternal and offspring caffeine PRSs and offspring phenotypes in childhood

		Maternal caffeine PRS analyses						Offspring caffeine PRS analyses					
		Regression analyses			Permutation testing			Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Specific phobia	OR	0.72	0.519, 1.012	0.057	0.019, 0.040	0.028	5,100	1.00	0.723, 1.381	0.997	0.993, 1.000	0.998	4,900
Depression	Beta	-0.02	-0.039, 0.002	0.075	0.056, 0.089	0.071	4,885	-0.02	-0.037, 0.002	0.081	0.055, 0.088	0.070	5,434
ADHD	Beta	-0.02	-0.008, 0.050	0.161	0.110, 0.152	0.130	4,916	-0.02	-0.046, 0.010	0.206	0.199, 0.251	0.224	5,219
Handedness	OR	1.06	0.968, 1.169	0.178	0.143, 0.189	0.165	4,849	0.98	0.897, 1.070	0.624	0.548, 0.610	0.579	5,399
Life events	Beta	-0.01	-0.007, 0.030	0.228	0.217, 0.271	0.243	5,167	-0.01	-0.027, 0.010	0.366	0.329, 0.390	0.359	5,493
ODD	Beta	0.002	-0.032, 0.008	0.240	0.257, 0.314	0.285	4,943	0.002	-0.018, 0.022	0.829	0.583, 0.644	0.614	5,319
Sleep initiation	OR	0.97	0.913, 1.036	0.352	0.316, 0.375	0.345	5,150	0.95	0.895, 1.010	0.094	0.059, 0.092	0.074	5,476
Total caffeine	Beta	0.01	-0.015, 0.032	0.490	0.444, 0.506	0.475	4,067	0.01	-0.012, 0.032	0.377	0.349, 0.410	0.379	4,589
BMI	Beta	0.03	-0.033, 0.084	0.387	0.364, 0.425	0.394	5,032	0.03	-0.027, 0.077	0.348	0.297, 0.356	0.326	5,799
Behavioural difficulties	Beta	-0.02	-0.019, 0.043	0.441	0.369, 0.431	0.400	5,133	-0.02	-0.044, 0.015	0.324	0.294, 0.353	0.323	5,452
Emotional problems	Beta	0.001	-0.014, 0.027	0.538	0.569, 0.631	0.600	5,139	0.001	-0.018, 0.021	0.883	0.881, 0.919	0.901	5,459
Sleep duration	Beta	-0.03	-0.030, 0.017	0.577	0.544, 0.606	0.575	5,127	-0.03	-0.048, -0.004	0.018	0.011, 0.028	0.018	5,443
CD	Beta	-0.01	-0.024, 0.015	0.624	0.627, 0.686	0.657	5,012	-0.01	-0.024, 0.013	0.563	0.541, 0.603	0.572	5,326
autism	OR	1.05	0.758, 1.461	0.742	0.733, 0.787	0.761	5,975	0.85	0.603, 1.199	0.326	0.307, 0.366	0.336	6,156
IQ	Beta	0.28	-0.521, 0.390	0.778	0.766, 0.817	0.792	4,675	0.28	-0.155, 0.707	0.209	0.183, 0.234	0.208	5,290
Anxiety	Beta	-0.02	-0.023, 0.019	0.849	0.805, 0.853	0.830	4,993	-0.02	-0.042, -0.002	0.029	0.017, 0.038	0.026	5,355
Sleep maintenance	OR	1.00	0.936, 1.071	0.970	0.947, 0.972	0.961	5,127	0.98	0.922, 1.048	0.573	0.517, 0.579	0.548	5,488

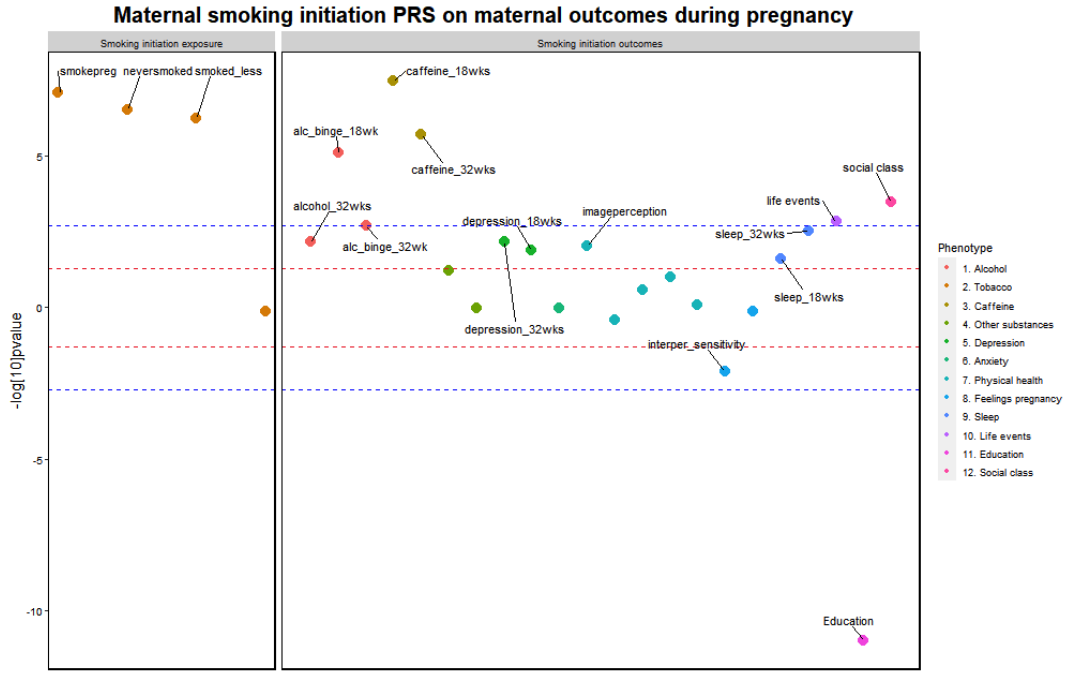
Note: OR-odds ratio; 95% CI – 95% confidence intervals

4.3.3 Aim 3: Maternal and offspring PRS associations on their own outcomes during and outside of pregnancy and adolescence

4.3.3.1 Smoking Initiation PRS

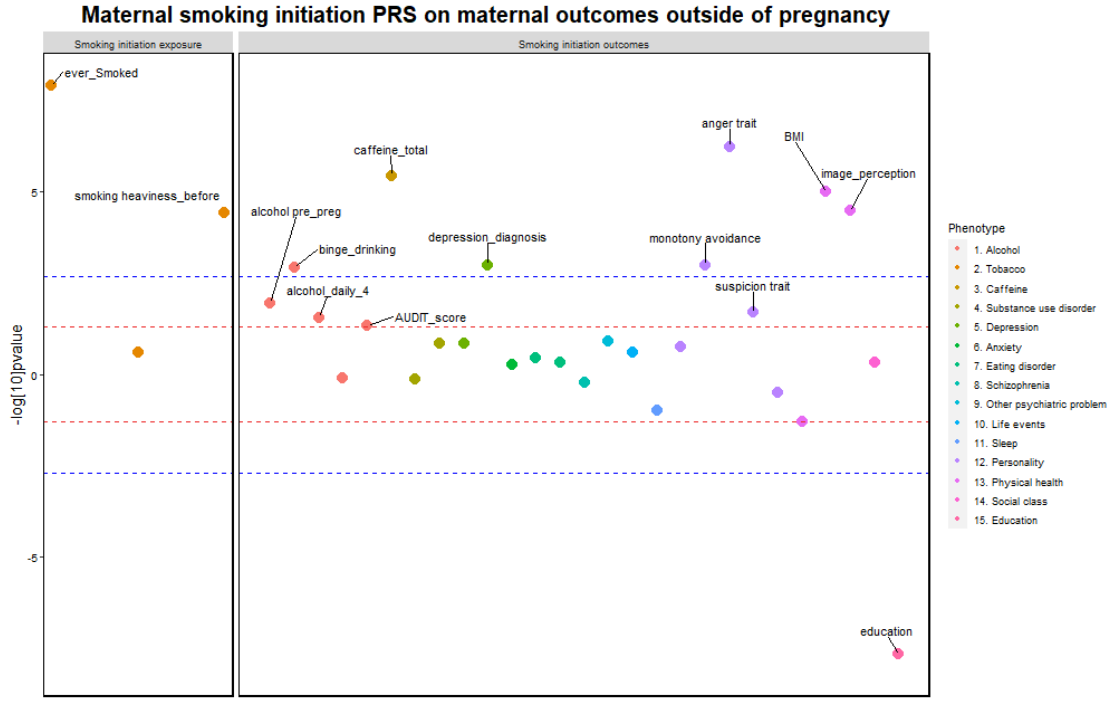
Maternal smoking initiation PRS on maternal outcomes during and outside of pregnancy: The associations between maternal smoking initiation PRS and maternal outcomes during and outside of pregnancy are shown in Figures 4.6 and 4.7 and Appendix 4.2. We found the strongest evidence (Bonferroni corrected) for non-mental health phenotypes, such as lower education and more negative image perception during and outside of pregnancy, higher anger, monotony avoidance and BMI outside of pregnancy, higher sensitivity to interpersonal rejection, and lower socioeconomic status during pregnancy. Among the substance use phenotypes, there was strong evidence for increased alcohol and caffeine consumption during and outside of pregnancy.

Figure 4.6. Associations between maternal smoking initiation PRS and maternal outcomes during pregnancy



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.002 after Bonferroni correction

Figure 4.7. Associations between maternal smoking initiation PRS and maternal outcomes outside of pregnancy

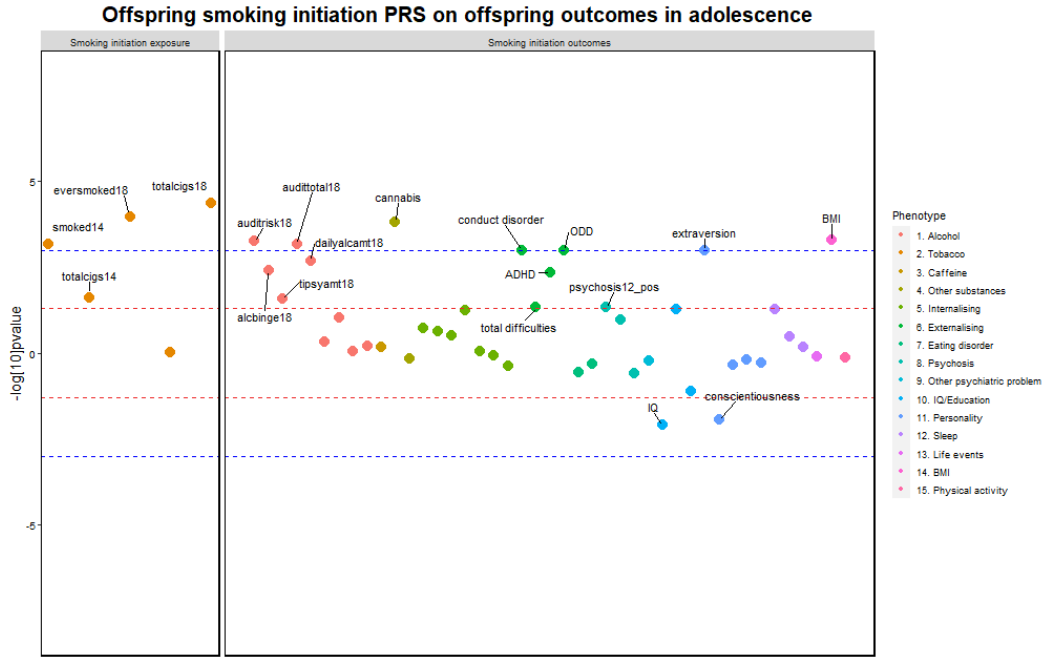


Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.002 after Bonferroni correction

Offspring smoking initiation PRS on offspring outcomes during adolescence: All results of the associations between offspring smoking initiation PRS and offspring outcomes during adolescence are shown in Figure 4.8 and Appendix 4.3.

Similarly to the results in childhood, offspring smoking initiation PRS showed the strongest evidence (Bonferroni corrected) for associations with mental health phenotypes such as increased conduct disorder symptoms. Furthermore, as in childhood, there was strong evidence for association with higher BMI in adolescence. Additionally, as in mothers, we observed associations for some personality traits in adolescence, such as higher extraversion. Among the substance use phenotypes, we observed strongest associations with increased alcohol and cannabis consumption in adolescence.

Figure 4.8. Associations between offspring smoking initiation PRS and offspring outcomes in adolescence



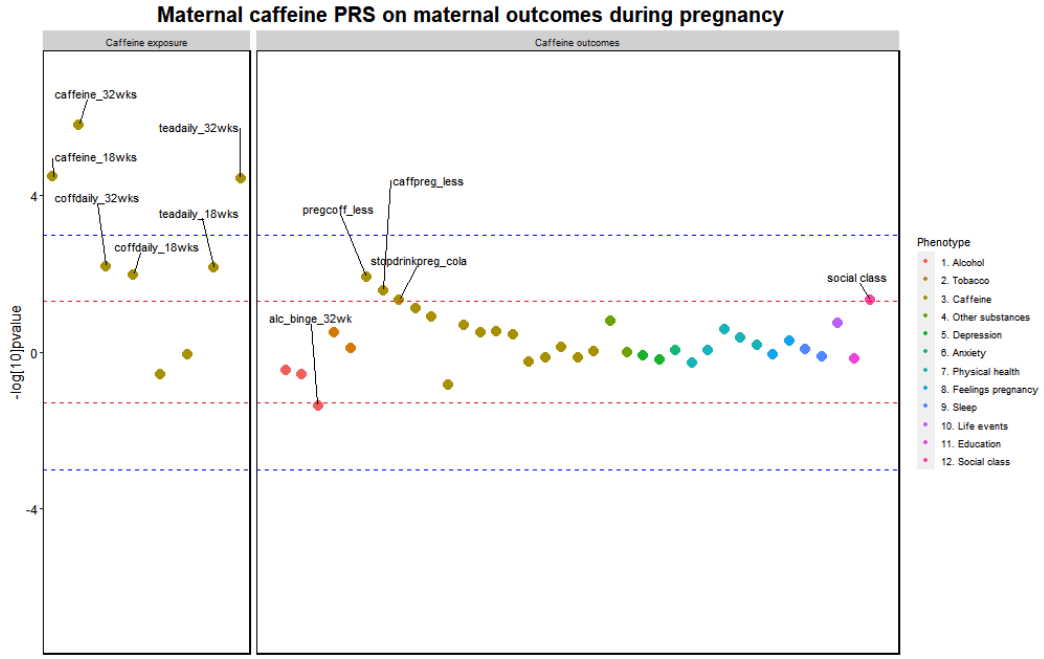
Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.001 after Bonferroni correction

4.3.3.2 Caffeine PRS

Maternal caffeine PRS on maternal outcomes during and outside of pregnancy: The associations between maternal caffeine PRS and maternal outcomes are shown in Figures 4.9 and 4.10 and Appendix 4.4.

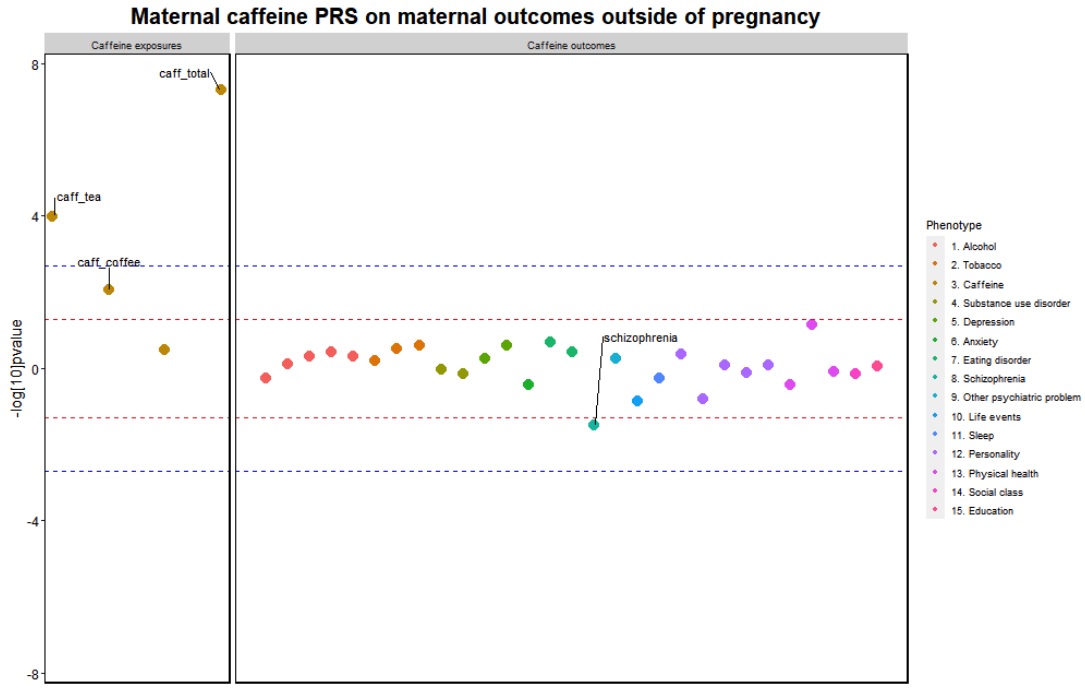
There was weak evidence for associations between maternal caffeine PRS and maternal mental health phenotypes. The only association we observed was with decreased likelihood of schizophrenia in mothers outside of pregnancy. However, there was some evidence for associations with non-mental health phenotypes, such as higher socioeconomical status during pregnancy. Additionally, among the substance use phenotypes, maternal caffeine PRS was associated with decreased binge drinking and higher likelihood of decreasing caffeine consumption during pregnancy. However, none of the associations survived Bonferroni correction.

Figure 4.9. Associations between maternal caffeine PRS and maternal outcomes during pregnancy



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.001 after Bonferroni correction

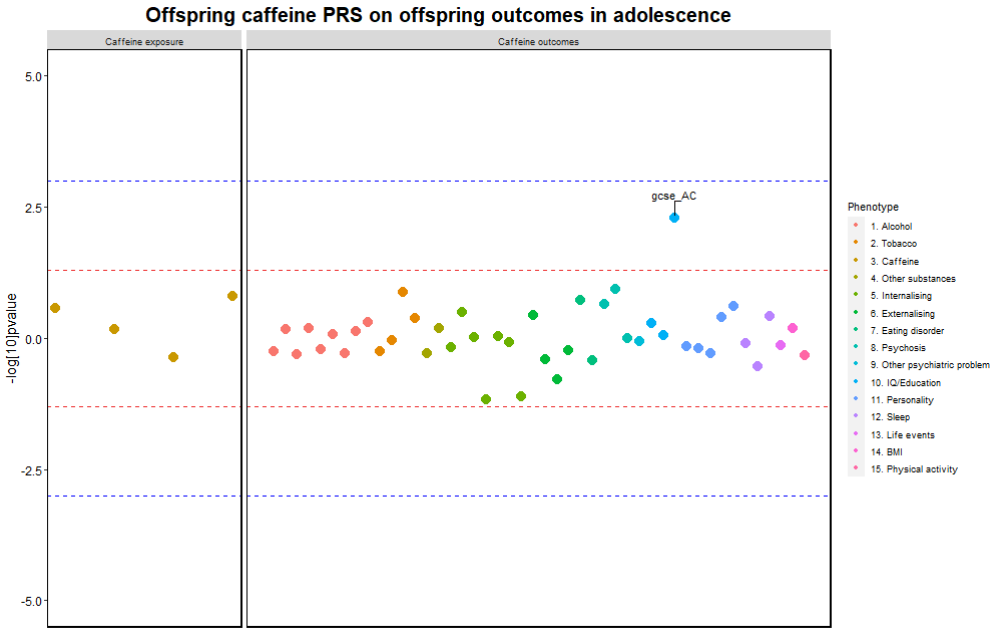
Figure 4.10. Associations between maternal caffeine PRS and maternal outcomes outside of pregnancy



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.002 after Bonferroni correction

Offspring caffeine PRS on offspring outcomes in adolescence: Associations between offspring caffeine PRS and offspring outcomes in adolescence are shown in Figure 4.11 and Appendix 4.5. The only evidence for an association in adolescence was observed for offspring caffeine PRS and higher GCSE exam grades, but this association did not survive Bonferroni correction.

Figure 4.11. Associations between offspring caffeine PRS and offspring outcomes in adolescence.



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.001 after Bonferroni correction

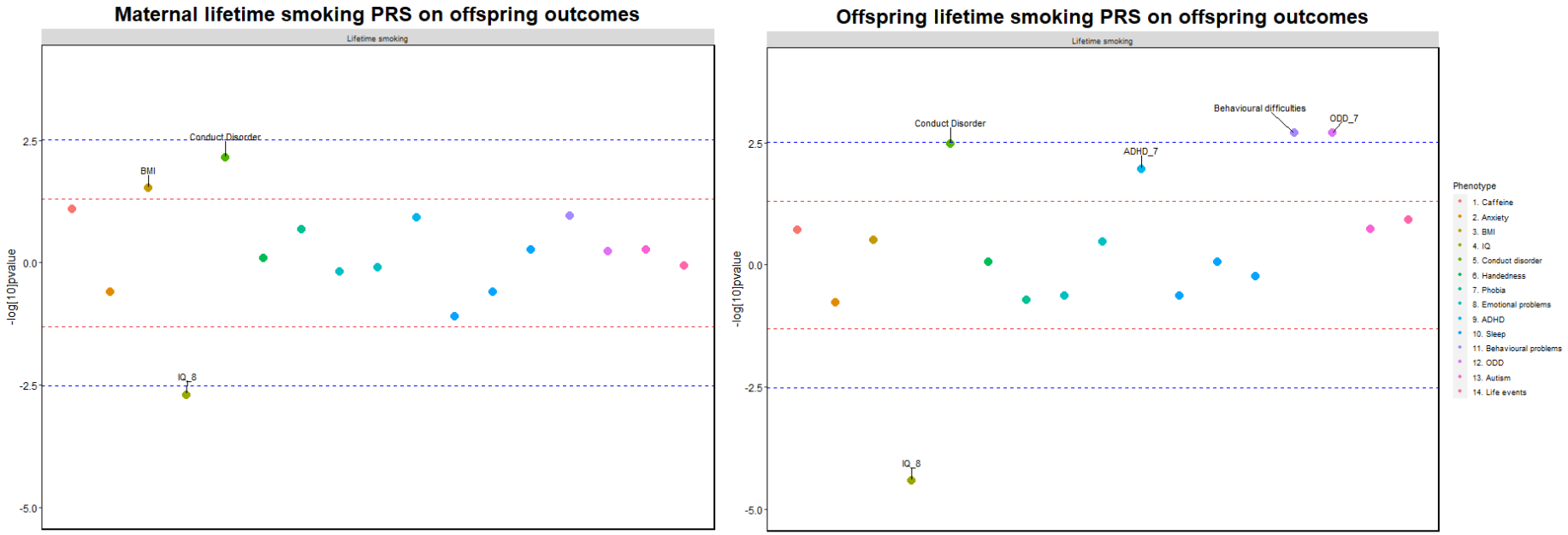
4.3.4 Sensitivity analyses

The results using the lifetime smoking PRS were mostly consistent with the results using the smoking initiation PRS. After applying Bonferroni correction, we found the strongest evidence for IQ in the maternal PRS analyses on offspring childhood outcomes, and ODD and total behavioural difficulties in the offspring PRS analyses on childhood outcomes. These results are shown in Figure 4.12 and Appendix 4.6.

The strongest evidence (Bonferroni corrected) in the maternal analyses during and outside pregnancy was observed for lower education during and outside of pregnancy, lower social class during pregnancy, increased anger and BMI outside of pregnancy, as well as with increased caffeine consumption during and outside of pregnancy. These results are shown in Figures 4.13 and 4.14 and in Appendix 4.7.

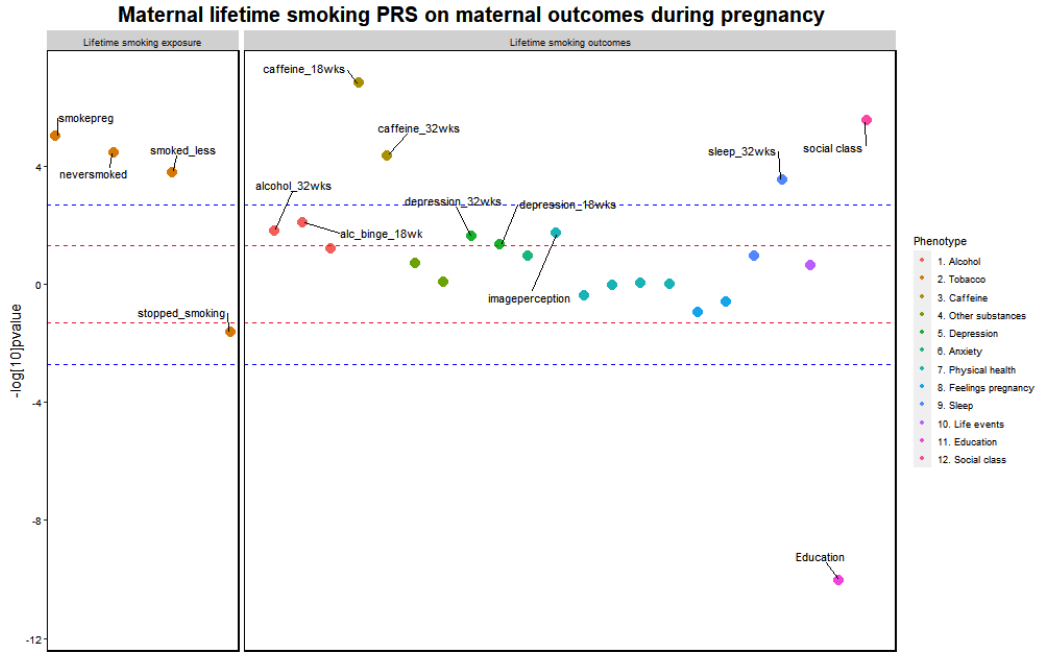
For the adolescence lifetime smoking PRS analysis, we found the strongest evidence (Bonferroni corrected) for higher conduct disorder symptoms and extraversion, as well as for lower IQ in adolescence. An overview of all the other results in adolescence using lifetime smoking PRS is shown in Figure 4.15 and Appendix 4.8.

Figure 4.12. Comparison of associations between maternal and offspring lifetime smoking PRSs on offspring outcomes in childhood



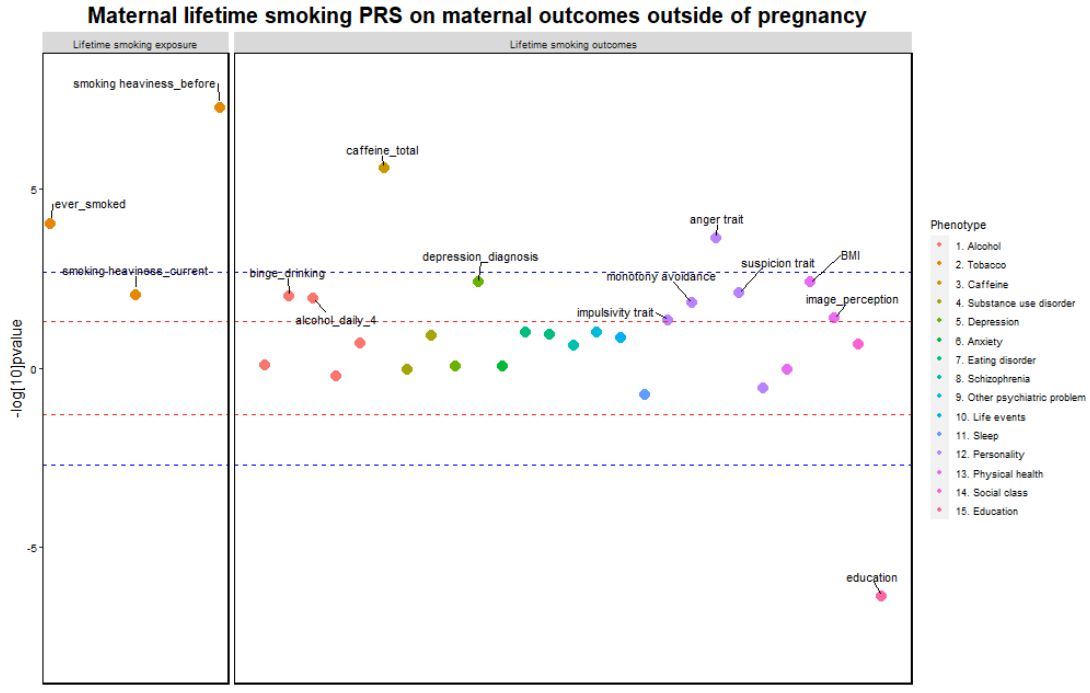
Note: Red dashed line shows threshold p<0.05 after permutation testing and blue dashed line shows threshold p<0.003 after Bonferroni correction

Figure 4.13. Associations between maternal lifetime smoking PRS and maternal outcomes during pregnancy



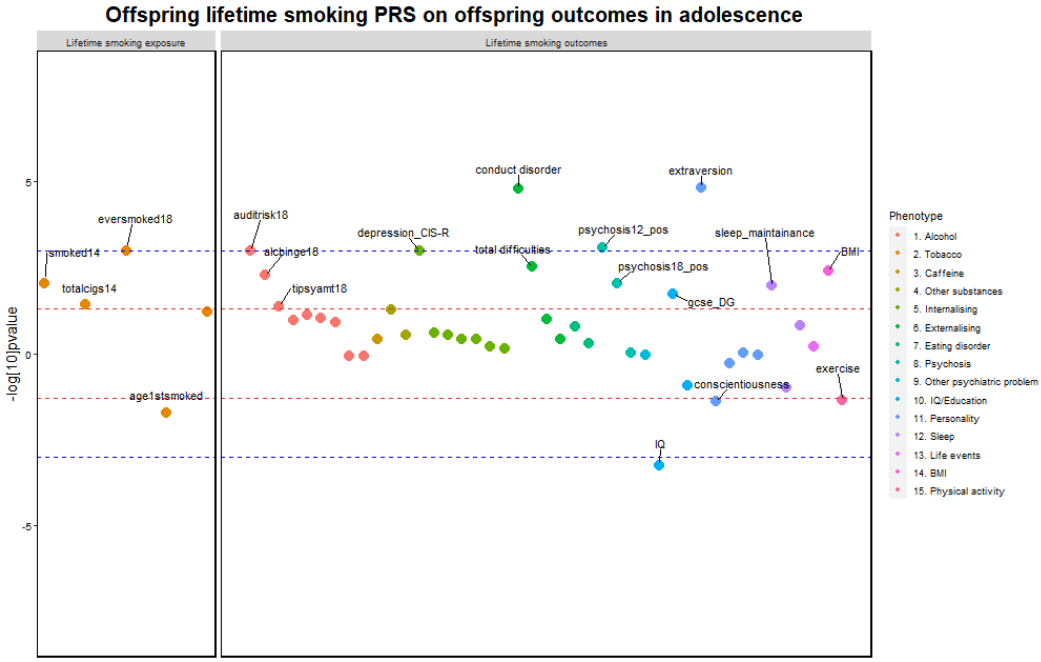
Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.002 after Bonferroni correction

Figure 4.14. Associations between maternal lifetime smoking PRS and maternal outcomes outside of pregnancy



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.002 after Bonferroni correction

Figure 4.15. Associations between offspring lifetime smoking PRS and offspring outcomes in adolescence



Note: Red dashed line shows threshold P<0.05 after permutation testing and blue dashed line shows threshold P<0.001 after Bonferroni correction

4.4 DISCUSSION

The main aim of this study was to investigate possible causal effects of maternal smoking and caffeine consumption on offspring mental health outcomes. Although the PheWAS design does not allow us to conclude directly which of the observed associations may be causally linked with mental health outcomes in offspring, by comparing different analyses across generations some inferences can be made.

Overall, these results showed that the smoking and caffeine PRS could be used as proxies for measuring smoking and caffeine consumption during pregnancy. However, caffeine PRS did not predict consumption in adolescence. Across generations, we observed several associations between smoking PRS and mental health outcomes. We found the strongest evidence for associations related to externalising behaviours and sensation-seeking traits, such as more behavioural problems in childhood and adolescence, more extroverted personality type, and increased alcohol consumption in mothers during pregnancy and offspring in adolescence. These findings indicate that intergenerational effects observed between maternal smoking PRS and offspring behavioural outcomes in childhood are likely to be pleiotropic. There was weaker statistical evidence for intergenerational effects of maternal caffeine PRS and offspring outcomes in childhood.

The literature supports findings of pleiotropic associations between the smoking PRS and sensation-seeking type of personality traits. Previous studies have found that adolescents who smoke have more externalising problems, higher impulsivity and novelty-seeking type of behaviours (Crone and Reijneveld, 2007) and that children with lower cognitive abilities have more behavioural problems and are more likely to initiate smoking themselves (Daly and Egan, 2017; Morin et al., 2017). Furthermore, there is evidence for shared genetic factors influencing smoking behaviours, externalising problems and novelty seeking type of behaviours (Stephens et al., 2012; Young et al., 2000), as well as educational attainment (Gage et al.,

2018). Some studies argue that the effect from the maternal postnatal environment (such as parenting behaviours) and mothers own mental health cannot be dismissed even after accounting for genetic effects (Eilertsen et al., 2020; Maughan et al., 2004).

The evidence for an association between the maternal smoking PRS and maternal depression during and outside of pregnancy may explain the association between the maternal smoking PRS and offspring externalising problems. However, a study using similar design (Easey et al., 2021) found an association between maternal PRS for increased alcohol consumption and maternal depression during pregnancy but did not find associations with offspring externalising problems. This could further support the conclusion that the associations observed between the smoking PRS and childhood externalising problems are pleiotropic. Furthermore, findings from other studies suggest that the smoking initiation PRS may not only capture smoking behaviour but also novelty-seeking and impulsive behaviours, even when only using genome-wide significant SNPs (Gage et al., 2018; Harrison et al., 2020). In addition, GSCAN summary statistics for smoking initiation showed a strong genetic correlation with ADHD and risk tolerance behaviour, which could make pleiotropic effects more likely (Liu et al., 2019). Given that smoking initiation is capturing more behaviours than just smoking, using the smoking initiation instrument in MR studies can be therefore problematic (Gage et al., 2020).

Taken together with the existing literature, our findings support the notion that the associations observed with the smoking initiation PRS are most likely explained by shared genetic liability in mothers and offspring. However, considering that a recent study conducted in the Norwegian Mother, Father and Child longitudinal birth cohort (MoBa) found some evidence for a maternal mental health effect on offspring ADHD symptoms even after accounting for genetic transmission, a maternal environmental effect cannot be completely ruled out (Eilertsen et al., 2020). Therefore, follow-up analyses are needed to further disentangle maternal environmental effects from pleiotropic effects.

The associations observed between the smoking initiation PRS and offspring BMI, caffeine consumption, and left-handedness were stronger in the maternal PRS analysis than in the offspring PRS analysis, which may reflect a causal effect. However, the associations with caffeine consumption and left-handedness are likely to be false positives, as these associations were not observed with lifetime smoking PRS and they did not survive Bonferroni correction.

Several studies have shown an association between maternal prenatal smoking and higher BMI in offspring (Magalhaes et al., 2019) which has been shown not to be affected by low birth weight (Beyerlein et al., 2011). However, findings from animal studies have indicated a negative association between prenatal smoke exposure on body weight (Jo et al., 2002). Further, other studies using negative control study designs have concluded that the association between maternal pre- and postnatal smoking and later childhood BMI is likely to be due to confounding rather than a causal intrauterine effect (Florath et al., 2014; Howe et al., 2012). Although a stronger association was observed between maternal smoking PRS on childhood BMI compared with offspring smoking PRS, analyses in mothers outside of pregnancy and adolescence showed consistently a positive association between smoking PRS on their own BMI. As previous studies using MR have found evidence for smoking decreasing BMI (Asvold et al., 2014; Taylor et al., 2019), it is plausible that findings in this study could be confounded through pleiotropic associations of the smoking initiation PRS or could be affected by maternal postnatal behaviour.

There was no strong evidence for intergenerational effects between maternal caffeine PRS and mental health outcomes in offspring in childhood, although we observed some interesting associations with the caffeine PRS across generations, such as higher social class in pregnancy, less anxiety in childhood and higher GCSE exam grades in adolescence. However, another study in secondary school students in the UK found a negative association between caffeine intake and school attendance (Richards and Smith, 2016), while a study in UK Biobank did not find an

association between coffee genetic risk score and socio-economic factors (Taylor, Davey Smith, et al., 2018). Therefore, these results should be interpreted with caution, as these findings could be false positives or unique to the ALSPAC sample.

The major strength of this study is the inter-generational approach, which enabled us to disentangle possible causal effects from pleiotropic effects by comparing observed associations in different sub-populations in ALSPAC. This includes 'negative control' approaches, by analysing phenotypes in childhood before their own consumption behaviour can influence the estimates, and together with other results can provide insights into potential causal effects. Furthermore, by using a PheWAS design, it was possible to include various mental health phenotypes, as well as other phenotypes to explore the complex nature of smoking and caffeine behaviour.

However, this study has also some limitations. First, due to the small sample size, we may have missed some associations. Second, not all the phenotypes were available across generations and therefore the comparison (externalising disorders in childhood and adolescence were compared with personality traits in adulthood) of phenotypes was not similar across sub-populations. Third, mental health phenotypes in childhood were mostly based on maternal report, which may not accurately reflect offspring's mental health problems (Gartstein et al., 2009; Najman et al., 2001) but instead mothers' own mental health status (Hennigan et al., 2006; Ringoot et al., 2015). Fourth, the smoking initiation PRS was derived from a GWAS that also included ALSPAC. Due to the sample overlap, the true strength of the observed associations might be smaller than we found. However, given the relatively small contribution of ALSPAC data to a total sample size of 1.2 million, the risk of bias is likely negligible. Fifth, to make the smoking PRS specific to exposures we based PRS on genome-wide significant SNPs only, but the smoking PRS still showed associations with some alcohol phenotypes, although the correlation between the smoking, caffeine and alcohol PRS was low (see Appendix 4.9). However, because of

the phenotypic associations with alcohol consumption, we cannot rule out that associations observed with the maternal smoking PRS are cofounded by maternal alcohol consumption. Still, because we did not find evidence for potential causal effects and no associations were observed between alcohol PRS and offspring mental health outcomes by Easey and colleagues (Easey et al., 2021), this is unlikely to affect observed results. Sixth, longitudinal cohort studies like ALSPAC may suffer from selection bias if the reasons why some participants drop out is not random (Munafò et al., 2018; Taylor, Jones, et al., 2018). Given that the dataset included phenotypes from later time points, with more missing data, it is possible that these findings are more subject to selection bias. Seventh, the maternal PRS analyses on offspring outcomes in childhood were based on transmitted alleles and therefore an indirect effect of maternal non-transmitted alleles on offspring behavioural outcomes through genetic nurturing cannot be ruled out (Kong et al., 2018).

To conclude, we found associations between maternal smoking PRS and externalising disorder symptoms in offspring. Although pleiotropic effects seem the more plausible explanation, no definitive conclusion can be drawn. Given that the PheWAS design does not allow inferring causality in a definitive way and analyses were affected by low statistical power, these findings need to be replicated in independent samples, ideally using methods robust to pleiotropy, such as MR.

4.5 CHAPTER SUMMARY

In this chapter I explained how a PheWAS design can be used to disentangle causal maternal environmental effects from pleiotropic effects by using data from different sub-populations in ALSPAC.

In the next chapter I will focus specifically on the ADHD phenotype, using negative control and MR approach to further examine a possible intrauterine effect of maternal prenatal smoking, alcohol and caffeine consumption on ADHD risk in offspring. In addition to the ALSPAC sample, I will use data from GenR and MoBa cohorts.

Chapter 5 PRENATAL SMOKING, ALCOHOL AND CAFFEINE EXPOSURE AND ADHD RISK IN CHILDHOOD: PARENTAL COMPARISONS AND POLYGENIC RISK SCORE (PRS) ANALYSES

This chapter is based on the manuscript "Prenatal smoking, alcohol and caffeine exposure and ADHD risk in childhood: parental comparisons and polygenic risk score (PRS) analyses." The preprint of this manuscript is available in medRxiv https://doi.org/10.1101/2021.03.25.21254087

Compared to Chapter 4, which examined associations between maternal and offspring smoking and caffeine PRS and various mental health outcomes, this chapter investigates whether there is a causal effect of maternal smoking, alcohol, and caffeine consumption during pregnancy on ADHD risk in offspring. I combined observational and genetic analyses and investigated whether there are different effects on ADHD hyperactive-impulsive and inattention symptom domains. In addition to data from ALSPAC, I also performed analyses using data from GenR and MoBa longitudinal birth cohorts.

5.1 INTRODUCTION

Many observational studies have shown that child symptoms and diagnosis of attention deficit hyperactivity disorder (ADHD) are associated with maternal smoking during pregnancy (He et al., 2020; Huang et al., 2018) and mixed findings have been reported for association with prenatal alcohol and caffeine exposure (Del-Ponte et al., 2016; Mikkelsen et al., 2017; Pagnin et al., 2019; Porter et al., 2019). However, inferring causality from associations between maternal prenatal substance use and offspring ADHD is challenging because the association could be affected by unmeasured shared familial factors that contribute to both maternal substance use during pregnancy and offspring ADHD. Several studies have shown genetic overlap between substance use and ADHD (Wimberley et al., 2020), and critically maternal genetic risk for ADHD has been found to be associated with smoking during pregnancy (Leppert et al., 2019).

Negative control designs (such as parental and sibling comparison) have been used to investigate potential causal intrauterine effects for a range of outcomes (Gage et al., 2016; Taylor et al., 2017). The main principle of the negative control approach is to compare the association of interest with another related association which is not biologically plausible (Gage et al., 2016). For example, in parental comparison mothers and fathers share the same confounding, but only mothers provide the intrauterine environment. If the maternal exposure-child outcome association is stronger, compared with the paternal exposure-child outcome association, this would suggest a potentially causal intrauterine effect. In contrast, if the magnitude of effect is similar, this would argue against a causal intrauterine effect, and instead suggest the association is due to confounding. An example where comparison of maternal and paternal effects has strengthened causal inference for an intrauterine effect is the relation between maternal smoking during pregnancy and low infant birth weight. In ALSPAC, a strong association was found between maternal smoking during pregnancy and infant birth weight, while paternal smoking during pregnancy showed only a weak association which almost disappeared when accounting for maternal smoking (Davey Smith, 2008).

Similarly, sibling comparison studies have been used to investigate potential intrauterine effects. These studies compare outcomes in siblings who are differentially exposed to maternal prenatal substance use which can account for shared environmental and genetic confounding. However, sibling comparison studies rely on the assumption that family environment remains stable and there are no other factors that vary between siblings and/or are highly correlated with both the exposure and outcome (D'Onofrio et al., 2013; Lewis et al., 2013).

Negative control designs have been used in the context of maternal substance use during pregnancy and offspring ADHD. A study based on the Danish National Birth Cohort and using parental comparison found evidence for a potential causal effect of maternal smoking during

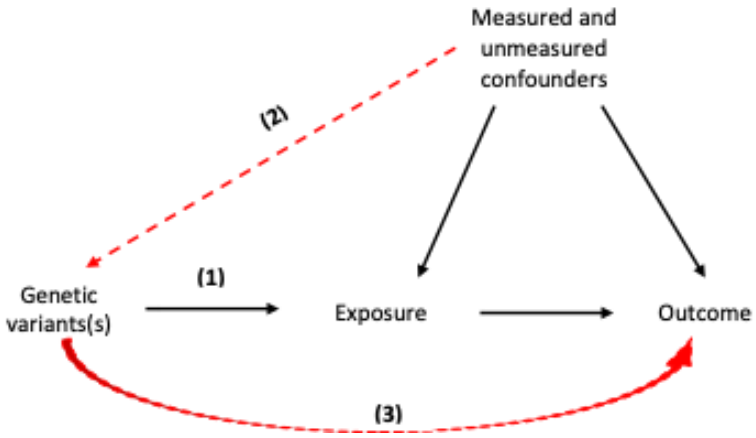
pregnancy on ADHD in offspring (Zhu et al., 2014). However, several other studies using negative control and other genetically sensitive designs have concluded that the association between maternal prenatal smoking and offspring ADHD is likely not causal (Rice et al., 2018; Skoglund et al., 2014). Sibling comparison studies on alcohol exposure based on the Norwegian Mother, Father and Child Cohort Study (MoBa) have found little evidence for a causal effect on ADHD symptoms (Eilertsen et al., 2017; Lund et al., 2019), although a sibling control analysis (Eilertsen et al) suggested some evidence for a potential causal effect on ADHD symptoms as measured by the Conner's Parent Rating Scale (CPRS-R). To my knowledge no negative control studies have been published on prenatal caffeine exposure and offspring ADHD.

Although published negative control studies investigating intrauterine effects have improved our understanding of whether a causal relationship exists, they may still be biased because of unmeasured and residual confounding. Using genetic variants in Mendelian Randomization (MR) analyses is an alternative approach that can strengthen causal inference. Genetic variants are randomly and independently assigned at conception and should therefore not be associated with factors that normally confound the exposure-outcome relationship or be subject to reverse causation, these methods could therefore provide stronger support for a potential causal effect (Lawlor et al., 2008).

Although in this study I did not use a formal MR approach to estimate the size of an effect of exposure on the outcome, I used polygenic risk score (PRS) analyses to look at whether a potential causal relationship exists. MR relies on three main assumptions: (1) relevance – the genetic variant must be robustly associated with the exposure of interest; (2) independence – the genetic variant is not confounded with the outcome or related through selection bias and (3) exclusion restriction – the genetic variant is not associated with the outcome by any other path than through the exposure of interest (Davies et al., 2018). These assumptions are relevant also in the PRS analyses deployed here. A visual overview of MR study design and

assumptions is shown in Figure 5.1. Assumptions 2 and 3 cannot be tested and, therefore, problems with horizontal pleiotropy – where the same genetic variant is directly associated with many phenotypes – confounding a genetic variant's relationship with the outcome or selection bias cannot be ruled out (Lawlor et al., 2008).

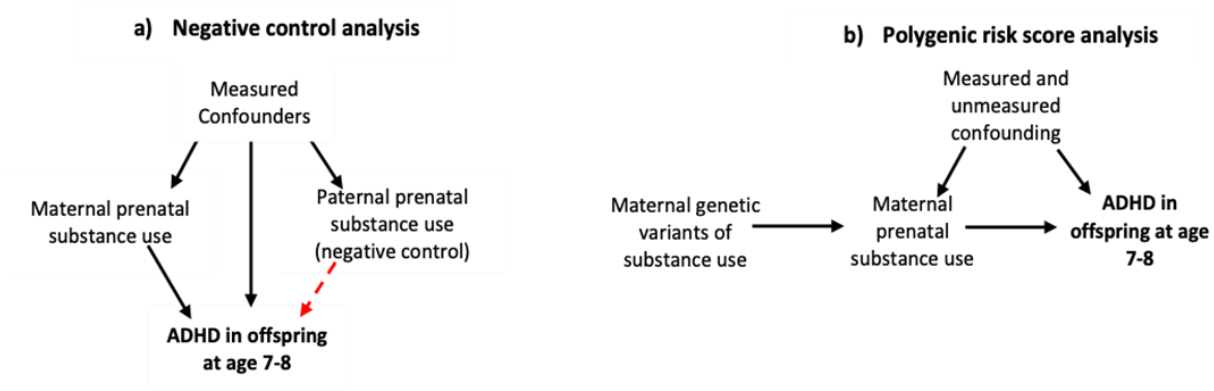
Figure 5.1. Overview of Mendelian Randomization design and assumptions



Note: Exposure is causally associated with the outcome if: (1) the genetic variant(s) is associated with the exposure; (2) the genetic variant is not associated with confounders; (3) the genetic variant is not independently associated with the outcome.

Combining multiple methodological approaches that rely on different assumptions and are subject to different sources of bias – known as triangulation – can strengthen causal inference (Munafò and Davey Smith, 2018). If results from multiple approaches with different sources of bias provide convergent results, it is more likely that the observed association reflects a causal effect (Lawlor et al., 2016). In this study, I combined the conventional multivariable regression approach, a negative control design using paternal prenatal substance use as a negative control, and genetic analyses using maternal PRS as a proxy for the exposures of interest. My aim was to investigate whether there is a causal effect of maternal substance use during pregnancy on high risk of offspring ADHD outcomes at age 7-8 years, using data from three large prospective birth cohorts. Overview of study design is shown in Figure 5.2

Figure 5.2. Overview of study design



Note: a) The red dashed arrow represents the negative control analysis. Assumptions include: the same confounders influence maternal and paternal prenatal substance use and offspring ADHD, a causal prenatal (intrauterine) effect only exists for maternal prenatal substance use. b) Polygenic risk score analysis was conducted with maternal genetic variants as proxies for prenatal smoking, alcohol, and caffeine consumption (3 separate analyses, with polygenic risk scores specific to the substance used).

5.2 METHODS

5.2.1 Study Population

I used data from three European prospective longitudinal birth cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC), the Generation R (GenR) and the Norwegian Mother, Father and Child Cohort Study (MoBa). More details about each cohort are given in Chapter 3 (see sections 3.2.1; 3.3.1 and 3.4.1)

5.2.2 Availability of genome-wide data

In ALSPAC, genome-wide data are available for 8,196 mothers. Maternal genetic data was not available for GenR at the time of analyses. In MoBa, genetic data are currently available for 14,584 mothers. Detailed information about the genotyping in the ALSPAC and MoBa cohorts is presented in Chapter 3 (see sections 3.2.2 and 3.4.2)

5.2.3 Exposures

Maternal smoking, alcohol and caffeine use during pregnancy were measured in each pregnancy trimester across all cohorts. Whereas paternal substance use was assessed only in the 2nd pregnancy trimester across all cohorts. I therefore used data assessed in the 2nd pregnancy trimester where information for both maternal and paternal substance use was available.

More details about exposure assessment in each cohort is given in Chapter 3 (see sections 3.2.4; 3.3.4 and 3.4.4).

Overall, exposure assessment was similar across the cohorts, but there were some exceptions in GenR. For example, paternal caffeine consumption during pregnancy was not measured, and maternal caffeine consumption was assessed only from coffee and tea. Further, paternal

smoking and alcohol use were assessed 2 months prior to their partner's pregnancy.

I categorized parental smoking, alcohol and caffeine consumption (from coffee and tea) during pregnancy to examine dose-dependent relationships. Smoking was categorized: No smoking; 1-4 cigarettes; 5-9 cigarettes and >10 cigarettes per day. Alcohol consumption was categorized: No drinking, <1 drink a week and 1-6 drinks a week. Only a small number of mothers drank daily, therefore these I combined with the group of weekly drinkers. Furthermore, because the measure of alcohol consumption is different in each cohort, I conducted a meta-analysis across the cohorts comparing drinkers and non-drinkers. However, in ALSPAC and MoBa I was able to harmonise weekly alcohol consumption from units to grams to create a continuous measure of alcohol consumption by multiplying units with corresponding grams. In ALSPAC, alcohol consumption was assessed continuously at 8 weeks of gestation. Caffeine consumption from coffee and tea was transformed and summed to total caffeine consumption in milligrams per day and categorized: 0-49mg; 50-199mg; 200-299mg and >300mg.

5.2.4 Outcome

In each cohort ADHD was measured using different questionnaires. Given that some studies have found that maternal substance use during pregnancy can have a distinct effect on ADHD hyperactive-impulsive and inattention symptom domains (Gard et al., 2016; Langley et al., 2007), I used questionnaires that measured total ADHD symptoms, as well as separately hyperactive-impulsive and inattention symptom domains.

5.2.4.1 Primary outcome measures

The psychometric scales I used for the main outcome measure at age 7-8 years were: maternal report of the Development And Well-Being Assessment (DAWBA) questionnaire in ALSPAC; maternal report of the revised Conner's Parent Rating Scale (CPRS-R) in GenR; and maternal report of the Disruptive Behavior Disorders scale (RS-DBD) in MoBa. All these

scales have shown good psychometric properties (Conners et al., 1998; Goodman et al., 2000; Silva et al., 2005). More details about these questionnaires in each cohort are provided in Chapter 3 (see sections 3.2.3.1; 3.3.3.1 and 3.4.3.1)

5.2.4.2 Secondary outcome measures

There is evidence of measurement differences between maternal and teacher reported ADHD symptoms in children (Narad et al., 2015), and some studies have also found conflicting results depending on the questionnaire used (Eilertsen et al., 2017). I therefore also included additional questionnaires, such as teacher report of the DAWBA questionnaire and maternal and teacher report of the Strengths and Difficulties Questionnaire (SDQ) hyperactivity subscale in ALSPAC and maternal and teacher report of the Child Behavior Checklist (CBCL) attention problems subscale in GenR to further explore if I observe different results depending on whether ADHD symptoms were reported by mother and/or teacher or which questionnaire was used. Psychometric properties of SDQ and CBCL are good (Goodman, 2001; Rishel et al., 2005), but these scales are broadband screeners and they do not distinguish ADHD symptom domains.

More details about the included secondary outcome measures are given in Chapter 3 (see sections 3.2.3.2 and 3.3.3.2)

5.2.5 Polygenic risk scores (PRSs)

I calculated PRSs using weighted sum of effect alleles based on genome-wide hits ($p<5x10^{-8}$). These were weighted by effect estimates as reported in the GWAS for tobacco, alcohol (Liu et al., 2019), and caffeine consumption (Cornelis et al., 2015) for mothers with genetic data available using PLINK v1.90 (Purcell et al., 2007). More details about the phenotypes and SNPs discovered in GWAS of smoking heaviness, alcohol and coffee consumption can be found in Table 5.1. Independent variants of smoking heaviness, alcohol and caffeine consumption were identified in the

discovery GWAS, and I therefore did not need to conduct further clumping or pruning (Choi et al., 2020).

Table 5.1. Phenotyping in genome-wide association studies

	GWAS phenotyping	SNPs
Smoking The GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) N=1.2 million	Smoking heaviness was defined as number of cigarettes individual smoked per day. Quantitative measure of cigarettes per day was binned to categories: 1-5; 6-15; 16-25; 26-35 and 36+ cigarettes per day. Studies with pre-defined bins were left the same.	55 SNPs were discovered to be conditionally independently associated with smoking heaviness at the genome-wide significance level ($p<5x10^{-8}$)
Alcohol (GSCAN)	Alcohol consumption was defined as number of drinks per week an individual consumed. As reporting of weekly alcohol consumption varied across the studies, binned response ranges were used (e.g., for 1-4 drinks per week, a midpoint was used). Phenotype was left-anchored at 1 and log-transformed before performing analysis to avoid effect from outliers	99 SNPs were associated with alcohol consumption at the genome-wide significance level
Coffee (The Coffee and Caffeine Genetics Consortium) N=91,462	Coffee data was collected categorically. Median value of each category was taken (e.g., for 2-3 cups per day, a 2.5 cups per day) for primary phenotype. Additionally, high/infrequent, and non-coffee consumers were compared ("phenotype 2")	8 SNPs were independently associated with cups of coffee consumed per day at the genome-wide level of significance*

**These SNPs have been also validated in caffeine consumption from other sources of caffeine besides coffee (McMahon et al., 2014; Treur et al., 2016)*

I calculated PRS for smoking heaviness with 49 SNPs available in ALSPAC and 51 SNPs available in MoBa and restricted the sample to smokers during pregnancy. I calculated PRS for alcohol consumption with 90 SNPs available in ALSPAC and 92 SNPs available in MoBa and I restricted the sample to mothers who drank during pregnancy. I calculated PRS for caffeine consumption with 8 SNPs available in ALSPAC and 7 SNPs available in MoBa. The range of PRS in ALSPAC and MoBa is shown in Table 5.2.

Table 5.2. The range of PRS in ALSPAC and MoBa

PRS	ALSPAC	MoBa
Smoking heaviness	-0.57 to 0.39	-0.65 to 0.37
Alcohol consumption	-0.23 to 0.23	-0.05 to 0.52
Caffeine consumption	-0.55 to 0.56	-0.53 to 0.42

There was little overlap between the SNPs included in the PRS for alcohol and caffeine, and no overlap between PRS for smoking and alcohol or caffeine. The correlation between these PRS were low ranging from -0.009 to 0.209 in ALSPAC and -0.013 to 0.217 in MoBa (shown in Tables 5.3 and 5.4).

Table 5.3. Correlation between PRSs in ALSPAC

	Alcohol consumption PRS	Smoking heaviness PRS	Lifetime smoking PRS
Smoking heaviness PRS	-0.005		
Lifetime smoking PRS	0.029	0.209	
Caffeine PRS	0.121	-0.007	-0.009

Note: Lifetime smoking PRS was included for sensitivity analyses (see section 5.2.6.3.2)

Table 5.4. Correlation between PRSs in MoBa

	Alcohol consumption PRS	Smoking heaviness PRS	Lifetime smoking PRS
Smoking heaviness PRS	-0.007		
Lifetime smoking PRS	0.043	0.217	
Caffeine PRS	0.128	-0.013	0.001

Note: Lifetime smoking PRS was included for sensitivity analyses (see section 5.2.6.3.2)

5.2.6 Statistical analysis

I performed all analyses using Stata (v15: ALSPAC, GenR; v16: MoBa), (StataCorp, 2017, 2019). Before I performed the analyses, I submitted a pre-registered protocol to the Open Science Framework (https://doi.org/10.17605/OSF.IO/WXU58). I conducted analyses separately in each cohort and then I meta-analysed results from primary outcome measure (maternal reported ADHD symptoms) across the cohorts using a random effects model. Compared to a fixed effects model which assumes that the true effect size is the same in all studies, a random effects model

estimates the mean effect in the range of studies by taking into account sample size differences, as well as the variance in the exposure and outcome assessment across the cohorts. Heterogeneity (the proportion of observed variance) between the cohorts was shown by computing I^2 (Borenstein et al., 2009).

I restricted the sample in each cohort to singletons in ALSPAC and GenR, whereas in MoBa I used a robust cluster variance estimator to account for the presence of siblings. Furthermore, in ALSPAC and GenR I restricted paternal analyses to individuals who were reported as biological fathers to optimise the validity of the same confounding structure, although still some non-paternity may exist. An overview of the sample used in the analyses for each cohort is shown in Chapter 3 (see section 3.5 “Cohorts comparison”).

5.2.6.1 Negative control analyses

I tested associations between maternal and paternal exposures and offspring outcome (dichotomised) using multivariable logistic regression analyses. I used three models: unadjusted (without including potential confounders); adjusted (for confounders identified a priori: child’s gender, ethnicity, parental age, education, depression and anxiety problems, financial difficulties, marital status and smoking, alcohol, and caffeine use) and mutually adjusted (adjusted for confounders and additionally adjusted for partner smoking, alcohol or caffeine use).

As there is evidence that mate selection is influenced by health behaviours such as smoking and alcohol use (Grant et al., 2007; Howe et al., 2019; Madley-Dowd et al., 2020; Taylor et al., 2017), mutually adjusted models are thought to produce the most valid estimates. Failure to account for assortative mating can increase bias in effect estimates and affect interpretation of study results (Madley-Dowd et al., 2020). A study by Madley-Dowd and colleagues showed that when assortative mating is increased then the difference in maternal and paternal effect estimates tends towards 0 leading to the conclusion of no difference, although the

effect may still exist. In contrast, effect estimates between maternal and paternal exposures are more similar after mutual adjustment.

I selected confounders based on the findings from previous studies (Gilman et al., 2008; Kovess et al., 2015; Langley et al., 2012; Russell, Ford, et al., 2015; Sagiv et al., 2013). In ALSPAC, maternal and paternal depression symptoms were measured using Edinburgh Postnatal Depressions Scale (EPDS) and anxiety symptoms with the anxiety sub-scale of the Crown-Crisp Experiential Index (CCEI). The scores were dichotomized, such as for the EPDS a validated cut-off score was ≥13 (Cox et al., 1996) and for the CCEI a threshold >85th percentile was used as in previous study in ALSPAC (Heron et al., 2004). In GenR, parental depression and anxiety symptoms were measured with the Brief Symptom Inventory (BSI). The cut-off score for maternal depression was 0.80 and for paternal depression was 0.71. For maternal anxiety the cut-off score was 0.71 and for fathers 0.65 (Elbert et al., 2017; Silva et al., 2019). In MoBa, parental depression and anxiety symptoms were measured with the Hopkins Symptoms Checklist-25 (SCL-25) and a cut-off score ≥2 was applied (Strand et al., 2003). Other included confounders were categorized as shown in Chapter 3 (see section 3.5 "Cohort comparison"). In MoBa, because of the longer recruitment period, I additionally adjusted analyses for birth year.

I meta-analysed results from the mutually adjusted model for smoking and alcohol consumption and the adjusted model for caffeine consumption (as paternal caffeine consumption was not assessed in GenR) in each of the three cohorts.

5.2.6.2 Polygenic risk score analyses

In ALSPAC and MoBa, I investigated the association between maternal PRSs and maternal exposure phenotypes, as well as with ADHD risk in offspring. I performed PRS analyses in both cohorts with adjustment for 10 ancestry-informative principal components. In MoBa, I additionally adjusted PRS analyses for birth year and genotyping batch as genotyping in MoBa was conducted in different batches. To explore potential pleiotropic effects, I

also tested the association between the PRSs, and each confounder included in the negative control analyses.

5.2.6.3 Sensitivity analyses

5.2.6.3.1 Negative control analyses

If I observed an association between maternal substance use during pregnancy and ADHD risk in offspring, I further tested the hypothesis of a potential intrauterine effect by comparing maternal substance use during pregnancy with substance use before pregnancy. If there is a stronger association found with substance use in pregnancy than before pregnancy, this may suggest a potential intrauterine effect.

Furthermore, given that ADHD is highly heritable, it is also plausible that any observed associations between maternal PRS and ADHD risk in offspring could be explained by genetic transmission. In MoBa, a measure of maternal ADHD was available, enabling me to test whether maternal ADHD could explain the observed associations between maternal exposures and ADHD symptoms in offspring. Maternal ADHD symptoms were measured at child age 5 years with the Adult ADHD Self-Report Scale (ASRS Screener). I dichotomised maternal ADHD symptoms score by using a validated cut-off score ≥13 (Kessler et al., 2007).

Finally, I also performed analyses with complete cases by restricting unadjusted and adjusted analyses to the sample in the mutually adjusted model for each exposure.

5.2.6.3.2 Polygenic risk score analyses

As well as weighted PRSs, I calculated unweighted PRSs to test the association with each exposure phenotype, given that SNPs selected based only on the genome-wide significance level may be biased upwards (the so-called Winner's Curse) (Shi et al., 2016). In addition to the PRS for smoking heaviness, I also included a PRS for lifetime smoking, which captures smoking initiation, duration, heaviness, and cessation, and can be used without stratifying samples on smoking status (Wootton et al., 2020). The

GWAS of lifetime smoking based on UK Biobank (N=462,690) identified 126 independent SNPs at the genome-wide level of significance ($p<5x10^{-8}$) (Wootton et al., 2020), of which 123 were available in ALSPAC and 121 SNPs in MoBa. The range of PRS for lifetime smoking in ALSPAC was -0.57 to 0.25 and in MoBa -0.52 to 0.36.

Finally, given that longitudinal studies may be subject to selection bias (Taylor, Jones, et al., 2018), I tested associations between PRSs for smoking, alcohol, and caffeine use and whether mothers returned the questionnaire at child age around 7-8 years in ALSPAC and MoBa.

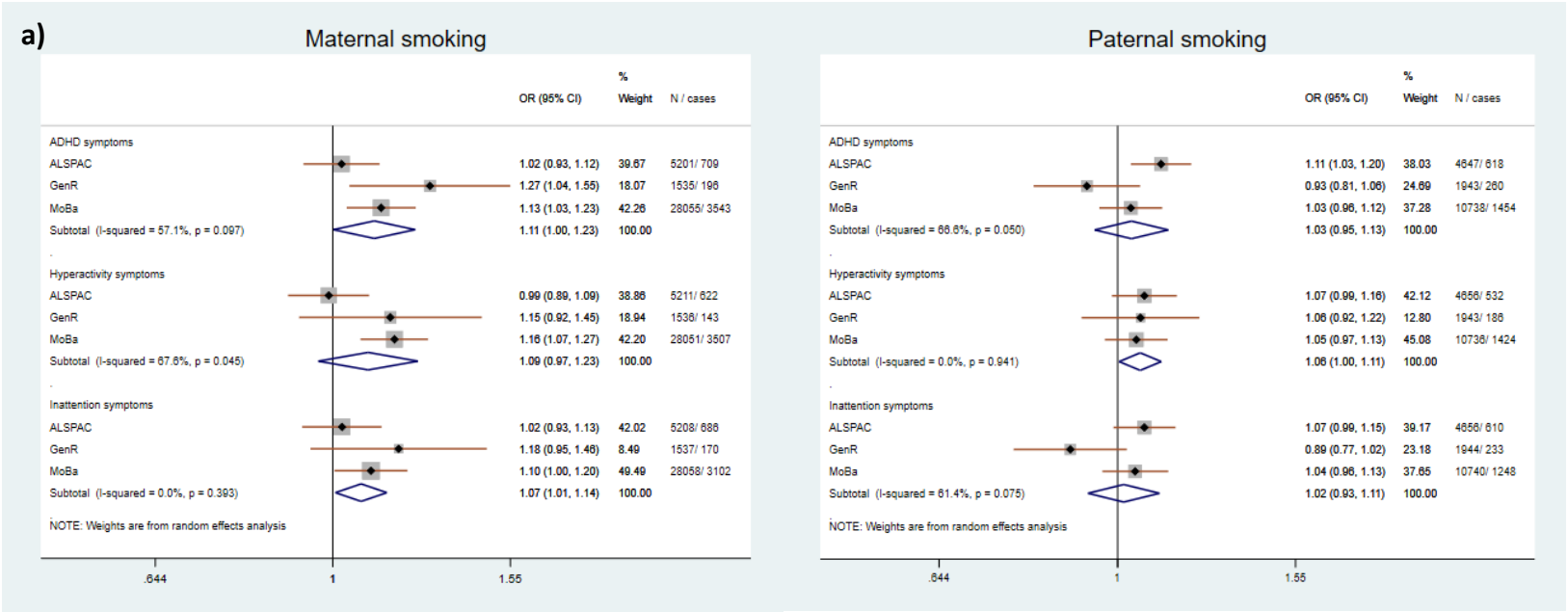
5.3 RESULTS

Overall, the negative control analyses comparing maternal and paternal substance use associations with offspring ADHD risk showed mixed evidence across the cohorts. I observed stronger associations in MoBa, where mothers had lower prenatal smoking, alcohol and caffeine consumption compared to mothers in ALSPAC and GenR.

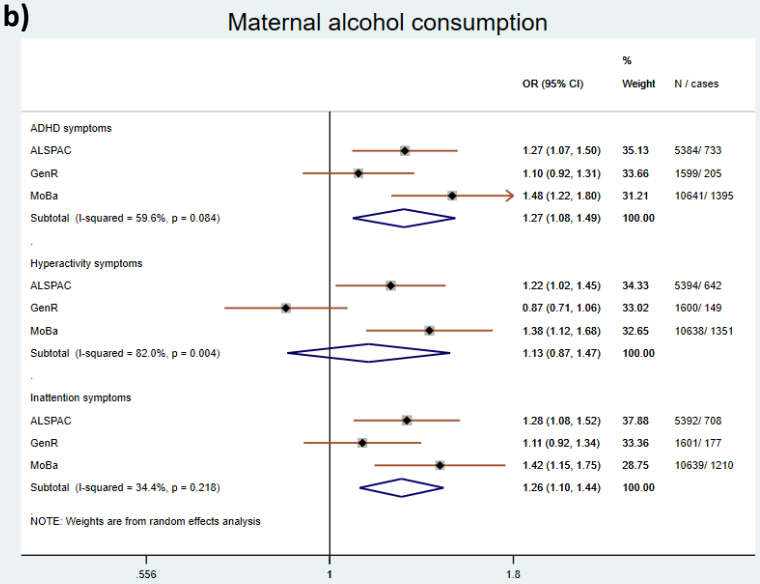
The results of meta-analysis across the cohorts are shown in Figure 5.3. The pooled estimates of maternal exposures were stronger compared with paternal exposures and although I did not formally test the difference between maternal and paternal exposures, their confidence intervals overlapped.

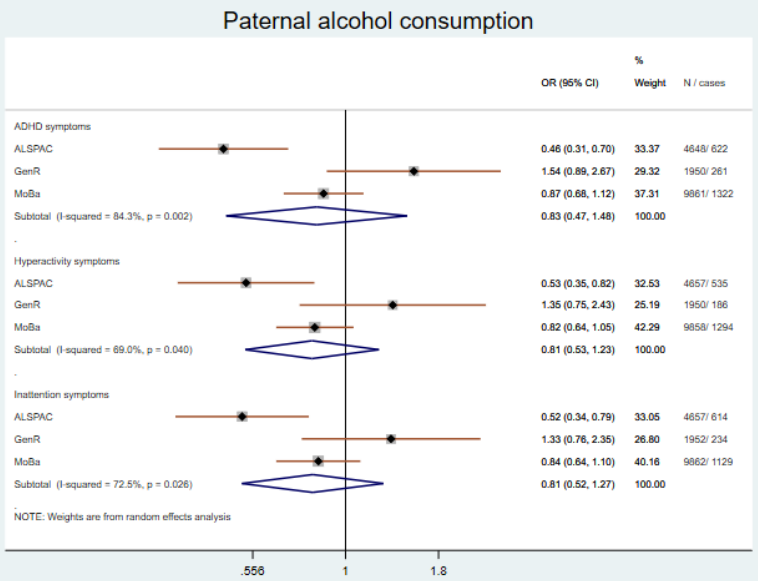
In contrast to the negative control analyses, my PRS analyses in ALSPAC and MoBa did not provide evidence for a causal effect of maternal smoking, alcohol, or caffeine consumption during pregnancy on ADHD risk in offspring. Furthermore, PRS analyses for lifetime smoking indicated pleiotropic associations with socio-demographic and mental health traits, as well as with participation in the study.

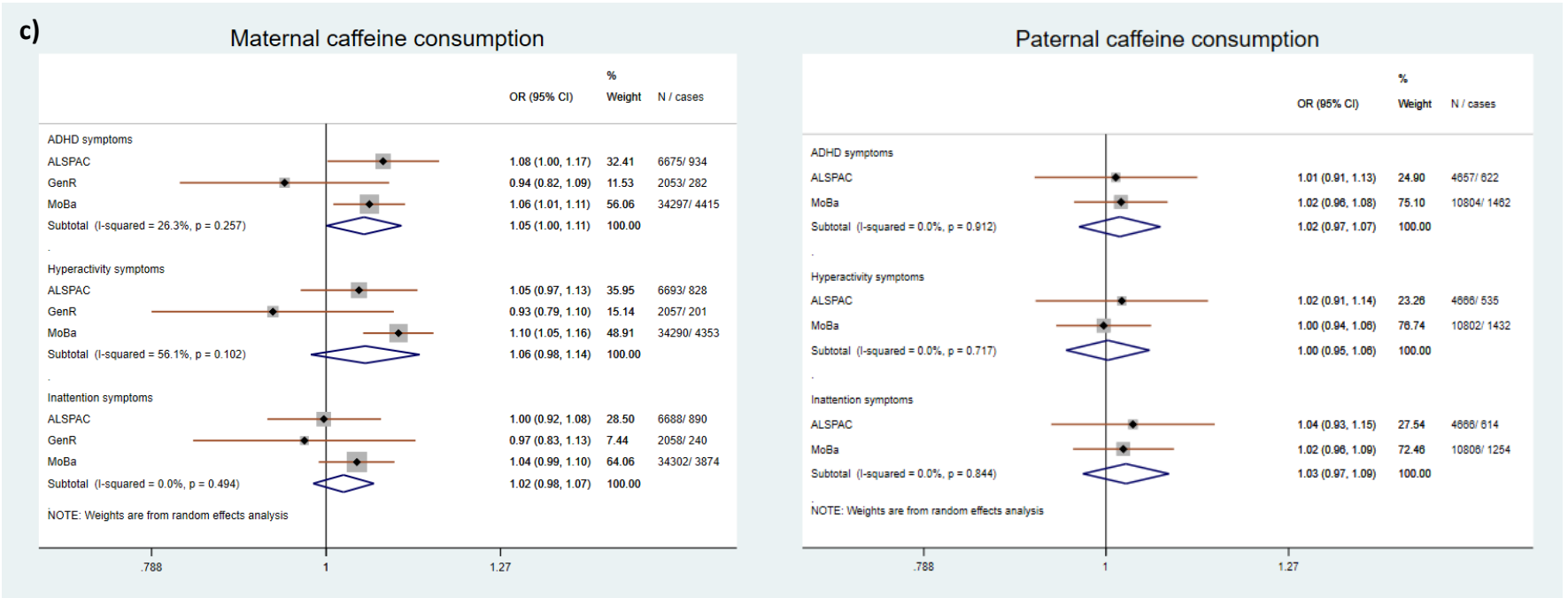
Figure 5.3. Meta-analysis of maternal and paternal prenatal smoking, alcohol, and caffeine consumption across the cohorts



b)


Maternal alcohol consumption
OR (95% CI)
% Weight
N / cases
ADHD symptoms
ALSPAC 1.27 (1.07, 1.50) 35.13 5384/ 733
GenR 1.10 (0.92, 1.31) 33.66 1599/ 205
MoBa 1.48 (1.22, 1.80) 31.21 10641/ 1395
Subtotal (I-squared = 59.6%, p = 0.084) 1.27 (1.08, 1.49) 100.00
Hyperactivity symptoms
ALSPAC 1.22 (1.02, 1.45) 34.33 5394/ 642
GenR 0.87 (0.71, 1.06) 33.02 1600/ 149
MoBa 1.38 (1.12, 1.68) 32.65 10638/ 1351
Subtotal (I-squared = 82.0%, p = 0.004) 1.13 (0.87, 1.47) 100.00
Inattention symptoms
ALSPAC 1.28 (1.08, 1.52) 37.88 5392/ 708
GenR 1.11 (0.92, 1.34) 33.36 1601/ 177
MoBa 1.42 (1.15, 1.75) 28.75 10639/ 1210
Subtotal (I-squared = 34.4%, p = 0.218) 1.26 (1.10, 1.44) 100.00
NOTE: Weights are from random effects analysis
.556
1
1.8


Paternal alcohol consumption
OR (95% CI)
% Weight
N / cases
ADHD symptoms
ALSPAC 0.46 (0.31, 0.70) 33.37 4648/ 622
GenR 1.54 (0.89, 2.67) 29.32 1950/ 261
MoBa 0.87 (0.68, 1.12) 37.31 9861/ 1322
Subtotal (I-squared = 84.3%, p = 0.002) 0.83 (0.47, 1.48) 100.00
Hyperactivity symptoms
ALSPAC 0.53 (0.35, 0.82) 32.53 4657/ 535
GenR 1.35 (0.75, 2.43) 25.19 1950/ 186
MoBa 0.82 (0.64, 1.05) 42.29 9858/ 1294
Subtotal (I-squared = 69.0%, p = 0.040) 0.81 (0.53, 1.23) 100.00
Inattention symptoms
ALSPAC 0.52 (0.34, 0.79) 33.05 4657/ 614
GenR 1.33 (0.76, 2.35) 26.80 1952/ 234
MoBa 0.84 (0.64, 1.10) 40.16 9862/ 1129
Subtotal (I-squared = 72.5%, p = 0.026) 0.81 (0.52, 1.27) 100.00
NOTE: Weights are from random effects analysis
.556
1
1.8



Note: Meta-analysis of smoking (a) and alcohol consumption (b) are based on mutually adjusted model. Meta-analysis of caffeine consumption (c) is based on adjusted model, because paternal caffeine consumption was not assessed in GenR. (see Methods section 5.2.6.1 for more details).

5.3.1 Smoking

5.3.1.1 Negative control analyses

The pooled estimate for maternal smoking in the mutually adjusted model provided weak evidence of an association with high risk of ADHD total and inattention symptoms (OR_{ADHD}=1.11, 95%CI 1.00, 1.23; OR_{INA}=1.07, 95%CI 1.01, 1.14). I observed a wide confidence interval for high risk of hyperactivity symptoms (OR_{HYP}=1.09, 95%CI 0.97, 1.23). For paternal smoking, unlike for maternal consumption, there was some evidence of an association with high risk of hyperactivity symptoms (OR_{HYP}=1.06, 95%CI 1.00, 1.11), but not with other ADHD outcomes (OR_{ADHD}=1.03, 95%CI 0.95, 1.13; OR_{INA}=1.02, 95%CI 0.93, 1.11). The results showing the dose-dependent relationship using non-smoking as baseline across unadjusted, adjusted and mutually adjusted models in each cohort are shown in Tables 5.5-5.7.

I observed stronger associations between maternal smoking and high risk of total ADHD symptoms in offspring compared with paternal smoking in GenR and MoBa; however, maternal and paternal confidence intervals overlapped. In ALSPAC, I found evidence of an association between paternal smoking and high risk of ADHD total symptoms (OR_{ADHD}=1.11, 95%CI 1.03, 1.20).

Table 5.5. Associations between maternal and paternal prenatal smoking and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (DAWBA)	7,731	1,114			<0.001	6,675	934			0.034	5,201	709			0.654
No cigarettes (ref)	6,256	822	-	-		5,483	701	-	-		4,319	542	-	-	
1-4 cigarettes	372	67	1.45	1.104,1.911		314	51	1.03	0.747,1.424		244	38	0.84	0.576,1.232	
5-9 cigarettes	367	68	1.50	1.144,1.976		301	60	1.26	0.922,1.734		228	44	1.07	0.734,1.553	
>10 cigarettes	736	157	1.79	1.481,2.170		577	122	1.27	0.990,1.617		410	85	1.07	0.797,1.449	
Hyperactive	7,751	984			<0.001	6,693	828			0.157	5,211	622			0.839
No cigarettes (ref)	6,274	726	-	-		5,499	628	-	-		4,329	486	-	-	
1-4 cigarettes	373	59	1.44	1.076,1.916		315	43	0.97	0.689,1.368		245	32	0.84	0.559,1.254	
5-9 cigarettes	366	64	1.62	1.223,2.144		300	54	1.27	0.913,1.754		227	35	0.98	0.652,1.463	
>10 cigarettes	738	135	1.71	1.398,2.094		579	103	1.16	0.896,1.501		410	69	0.98	0.715,1.348	
Inattentive	7,743	1,058			<0.001	6,688	890			0.098	5,208	686			0.651
No cigarettes (ref)	6,266	810	-	-		5,494	690	-	-		4,326	541	-	-	
1-4 cigarettes	372	54	1.14	0.849,1.541		314	44	0.94	0.670,1.321		243	31	0.73	0.487,1.099	
5-9 cigarettes	368	62	1.37	1.029,1.811		302	52	1.20	0.863,1.670		228	39	1.06	0.721,1.568	
>10 cigarettes	737	132	1.47	1.201,1.799		578	104	1.22	0.947,1.581		411	75	1.09	0.802,1.488	
ADHD (SDQ)	7,994	892			<0.001	6,946	737			0.029	5,405	561			0.159
No cigarettes (ref)	6,421	639	-	-		5,672	545	-	-		4,459	415	-	-	
1-4 cigarettes	386	57	1.57	1.170,2.101		323	45	1.26	0.899,1.767		249	35	1.17	0.792,1.732	
5-9 cigarettes	380	51	1.40	1.033,1.905		317	38	0.97	0.669,1.397		238	28	0.88	0.568,1.358	
>10 cigarettes	807	145	1.98	1.627,2.414		634	109	1.37	1.060,1.762		459	83	1.30	0.963,1.764	

	Paternal														
ADHD (DAWBA)	5,841	815			<0.001	4,657	622			0.001	4,647	618			0.005
No cigarettes (ref)	3,977	474	-	-		3,288	382	-	-		3,284	381	-	-	
1-4 cigarettes	296	47	1.40	1.007,1.933		237	35	1.21	0.825,1.787		235	34	1.18	0.799,1.755	
5-9 cigarettes	254	46	1.63	1.171,2.281		185	29	1.29	0.846,1.978		184	28	1.24	0.803,1.912	
>10 cigarettes	1,314	248	1.72	1.453,2.034		947	176	1.44	1.159,1.790		944	175	1.38	1.097,1.730	
Hyperactive	5,851	711			<0.001	4,666	535			0.042	4,656	532			0.105
No cigarettes (ref)	3,983	427	-	-		3,295	341	-	-		3,291	340	-	-	
1-4 cigarettes	297	38	1.22	0.857,1.743		237	29	1.16	0.764,1.753		235	28	1.112	0.728,1.700	
5-9 cigarettes	254	29	1.07	0.720,1.601		184	16	0.73	0.427,1.248		183	16	0.727	0.424,1.248	
>10 cigarettes	1,317	217	1.64	1.377,1.961		950	149	1.31	1.043,1.652		947	148	1.262	0.991,1.606	
Inattentive	5,849	478			<0.001	4,666	614			0.065	4,656	610			0.089
No cigarettes (ref)	3,979	45	-	-		3,293	394	-	-		3,289	393	-	-	
1-4 cigarettes	299	41	1.30	0.932,1.807		239	37	1.24	0.847,1.806		237	36	1.24	0.841,1.817	
5-9 cigarettes	254	215	1.41	0.996,1.996		185	27	1.15	0.743,1.776		184	26	1.13	0.723,1.760	
>10 cigarettes	1,317	779	1.43	1.200,1.702		949	156	1.23	0.981,1.530		946	155	1.22	0.966,1.538	
ADHD (SDQ)	6,030	646			0.099	4,804				0.094	4,793				0.023
No cigarettes (ref)	4,059	373	-	-		3,358	289	-	-		3,353	289	-	-	
1-4 cigarettes	307	37	1.35	0.945,1.940		241	30	1.42	0.942,2.144		239	29	1.32	0.869,2.013	
5-9 cigarettes	268	32	1.34	0.912,1.968		196	23	1.26	0.795,2.004		195	23	1.22	0.762,1.937	
>10 cigarettes	1,396	204	1.69	1.409,2.030		1,009	145	1.48	1.171,1.868		1,006	144	1.33	1.036,1.699	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partners' prenatal smoking*

Table 5.6. Associations between maternal and paternal prenatal smoking and high risk of maternal and teacher reported offspring ADHD symptoms in GenR

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
Maternal															
ADHD (CPRS-R)	3,116	452			<0.001	2,053	282			0.023	1,535	196			0.018
No cigarettes (ref)	2,471	330	-	-		1,623	209	-	-		1,219	145	-	-	
1-4 cigarettes	358	62	1.36	1.009,1.829		226	32	1.02	0.666,1.548		165	21	1.01	0.592,1.720	
5-9 cigarettes	159	29	1.45	0.952,2.200		113	18	1.13	0.649,1.974		82	13	1.26	0.639,2.484	
>10 cigarettes	128	31	2.07	1.361,3.158		91	23	1.97	1.144,3.375		69	17	2.48	1.293,4.755	
Hyperactive	3,119	345			0.007	2,057	201			0.076	1,536	143			0.217
No cigarettes (ref)	2,475	260	-	-		1,628	152	-	-		1,221	107	-	-	
1-4 cigarettes	358	41	1.10	0.777,1.563		226	20	0.93	0.560,1.548		165	14	0.77	0.413,1.440	
5-9 cigarettes	158	20	1.24	0.759,1.563		112	12	1.05	0.544,2.014		81	9	0.97	0.445,2.123	
>10 cigarettes	128	24	1.97	1.239,3.121		91	17	1.99	1.079,3.663		69	13	1.99	0.964,4.099	
Inattentive	3,117	391			0.039	2,058	240			0.288	1,537	170			0.143
No cigarettes (ref)	2,472	298	-	-		1,628	188	-	-		1,221	133	-	-	
1-4 cigarettes	358	49	1.16	0.836,1.601		226	21	0.72	0.444,1.183		165	15	0.81	0.442,1.470	
5-9 cigarettes	159	19	0.99	0.604,1.623		113	10	0.65	0.323,1.293		82	7	0.68	0.292,1.589	
>10 cigarettes	128	25	1.77	1.125,2.787		91	21	2.01	1.154,3.513		69	15	2.49	1.259,4.932	
ADHD (CBCL)	4,168	595			<0.001	2,565	331			0.004	1,835	211			0.031
No cigarettes (ref)	3,199	396	-	-		1,970	217	-	-		1,432	140	-	-	
1-4 cigarettes	521	99	1.66	1.303,2.117		306	54	1.47	1.040,2.090		211	31	1.22	0.770,1.942	
5-9 cigarettes	255	60	2.18	1.601,2.963		161	31	1.35	0.858,2.132		107	21	1.53	0.863,2.725	
>10 cigarettes	193	40	1.85	1.286,2.662		128	29	1.76	1.086,2.846		85	19	1.80	0.972,3.323	
ADHD (TRF)	3,023				<0.001	1,671	218			0.002	1,148	125			0.059
No cigarettes (ref)	2,247	307	-	-		1,253	142	-	-		878	85	-	-	
1-4 cigarettes	420	76	1.40	1.059,1840		221	33	1.25	0.802,1.944		141	16	1.01	0.529,1.908	
5-9 cigarettes	207	52	2.12	1.514,2.968		117	25	2.24	1.302,3.849		75	12	1.59	0.737,3.449	
>10 cigarettes	149	27	1.40	0.906,2.158		80	18	2.03	1.087,3.806		54	12	2.16	0.944,4.918	

								Paternal							
ADHD (CPRS-R)	2,381	333			0.882	2,117	289			0.220	1,930	260			0.237
No cigarettes (ref)	1,412	197	-	-		1,249	170	-	-		1,148	149	-	-	
1-4 cigarettes	387	52	0.96	0.689,1.330		355	46	0.85	0.588,1.214		328	43	0.89	0.606,1.310	
5-9 cigarettes	166	26	1.15	0.734,1.787		148	21	0.80	0.476,1.334		132	20	0.87	0.502,1.518	
>10 cigarettes	416	58	1.00	0.729,1.370		365	52	0.82	0.574,1.176		322	48	0.79	0.522,1.180	
Hyperactive	2,381	241			0.031	2,117	202			0.193	1,930	186			0.448
No cigarettes (ref)	1,412	130	-	-		1,249	104	-	-		1,148	98	-	-	
1-4 cigarettes	386	39	1.11	0.760,1.616		354	35	1.12	0.735,1.696		327	31	1.09	0.695,1.704	
5-9 cigarettes	166	19	1.28	0.765,2.124		148	15	0.97	0.527,1.766		132	15	1.12	0.598,2.106	
>10 cigarettes	417	53	1.44	1.022,2.017		366	48	1.33	0.901,1.974		323	42	1.18	0.757,1.852	
Inattentive	2,382	290			0.661	2,119	256			0.024	1,931	233			0.078
No cigarettes (ref)	1,412	174	-	-		1,250	156	-	-		1,149	139	-	-	
1-4 cigarettes	386	47	0.99	0.699,1.391		354	42	0.86	0.593,1.259		327	40	0.94	0.633,1.401	
5-9 cigarettes	166	22	1.09	0.675,1.749		148	17	0.71	0.406,1.240		132	17	0.91	0.506,1.621	
>10 cigarettes	418	47	0.90	0.640,1.269		367	41	0.66	0.443,0.969		323	37	0.66	0.423,1.024	
ADHD (CBCL)	2,913	366			<0.001	2,541	305			0.025	2,323	275			0.039
No cigarettes (ref)	1,689	177	-	-		1,478	148	-	-		1,361	130	-	-	
1-4 cigarettes	458	61	1.31	0.961,1.792		414	54	1.29	0.911,1.826		381	49	1.32	0.914,1.919	
5-9 cigarettes	220	33	1.51	1.009,2.252		183	26	1.20	0.747,1.921		164	25	1.33	0.807,2.195	
>10 cigarettes	546	95	1.80	1.373,2.358		466	77	1.45	1.051,1.994		417	71	1.46	1.011,2.093	
ADHD (TRF)	1,876	214			0.005	1,570	166			0.230	1,445	151			0.347
No cigarettes (ref)	1,045	100	-	-		883	77	-	-		816	68	-	-	
1-4 cigarettes	306	36	1.26	0.841,1.888		264	30	1.23	0.758,1.992		242	29	1.41	0.851,2.344	
5-9 cigarettes	157	27	1.96	1.235,3.118		121	18	1.28	0.703,2.314		109	17	1.52	0.806,2.876	
>10 cigarettes	368	51	1.52	1.060,2.180		302	41	1.29	0.827,2.015		278	37	1.21	0.732,2.002	

*Note: CPRS-R – Revised Conners' Parent Rating Scale; CBCL – Child Behavior Checklist; TRF – Teacher Report Form; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, parity, parental ethnicity, age, education, anxiety and depression symptoms, financial difficulties, parental alcohol and prenatal caffeine consumption; **additionally adjusted for partner's smoking*

Table 5.7. Associations between maternal and paternal prenatal smoking and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (RS-DBD)	41,515	5,509			<0.001	34,297	4,415			<0.001	28,055	3,543			0.006
No cigarettes (ref)	39,162	4,993	-	-		32,487	4,035	-	-		26,706	3,280	-	-	
1-4 cigarettes	1,260	234	1.56	1.350,1.805		951	168	1.13	0.946,1.360		707	111	0.95	0.761,1.182	
5-9 cigarettes	650	158	2.20	1.830,2.640		501	121	1.66	1.326,2.075		383	87	1.49	1.136,1.941	
>10 cigarettes	443	124	2.66	2.159,3.277		358	91	1.50	1.149,1.945		259	65	1.38	1.000,1.893	
Hyperactive	41,508	5,436			<0.001	34,290	4,353			<0.001	28,051	3,507			<0.001
No cigarettes (ref)	39,158	4,916	-	-		32,483	3,971	-	-		26,704	3,232	-	-	
1-4 cigarettes	1,259	239	1.63	1.414,1.883		950	166	1.16	0.968,1.384		707	117	1.04	0.840,1.286	
5-9 cigarettes	649	159	2.26	1.884,2.712		500	124	1.75	1.409,2.185		382	91	1.60	1.228,2.073	
>10 cigarettes	442	122	2.66	2.152,3.278		357	92	1.57	1.208,2.036		258	67	1.45	1.061,1.991	
Inattentive	41,524	4,824			<0.001	34,302	3,874			0.001	28,058	3,102			0.041
No cigarettes (ref)	39,170	4,402	-	-		32,491	3,551	-	-		26,708	2,877	-	-	
1-4 cigarettes	1,261	198	1.47	1.259,1.719		952	151	1.14	0.940,1.373		708	101	0.99	0.783,1.243	
5-9 cigarettes	650	131	1.99	1.640,2.423		501	102	1.53	1.208,1.935		383	70	1.32	0.996,1.760	
>10 cigarettes	443	93	2.10	1.663,2.648		358	70	1.24	0.924,1.661		259	54	1.31	0.929,1.837	

								Paternal							
ADHD (RS-DBD)	33,955	4,397			<0.001	10,804	1,462			0.155	10,738	1,454			0.417
No cigarettes (ref)	26,918	3,312	-	-		9,018	1,198	-	-		8,965	1,193	-	-	
1-4 cigarettes	3,252	436	1.10	0.991,1.229		1,001	122	0.86	0.702,1.050		998	120	0.83	0.680,1.021	
5-9 cigarettes	870	140	1.37	1.134,1.648		213	41	1.40	0.980,1.994		211	40	1.32	0.919,1.889	
>10 cigarettes	2,915	509	1.51	1.360,1.672		572	101	1.17	0.917,1.484		564	101	1.09	0.846,1.404	
Hyperactive	33,951	4,370			<0.001	10,802	1,432			0.082	10,736	1,424			0.242
No cigarettes (ref)	26,917	3,284	-	-		9,017	1,162	-	-		8,964	1,157	-	-	
1-4 cigarettes	3,252	434	1.11	0.995,1.234		1,000	134	1.00	0.822,1.217		997	132	0.98	0.801,1.190	
5-9 cigarettes	870	133	1.30	1.073,1.572		213	40	1.41	0.988,2.020		211	39	1.35	0.939,1.945	
>10 cigarettes	2,912	519	1.56	1.408,1.730		572	96	1.14	0.893,1.459		564	96	1.09	0.843,1.411	
Inattentive	33,958	3,851			<0.001	10,806	1,254			0.133	10,740	1,248			0.295
No cigarettes (ref)	26,923	2,922	-	-		9,019	1,023	-	-		8,966	1,018	-	-	
1-4 cigarettes	3,251	383	1.10	0.979,1.229		1,001	111	0.92	0.741,1.131		998	110	0.90	0.727,1.115	
5-9 cigarettes	869	122	1.34	1.102,1.633		213	31	1.18	0.794,1.746		211	31	1.16	0.784,1.725	
>10 cigarettes	2,915	424	1.40	1.253,1.560		573	89	1.21	0.937,1.560		565	89	1.16	0.887,1.509	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partner's smoking*

5.3.1.1.1 Sensitivity analyses

In MoBa, additional adjustment for maternal ADHD attenuated the association between prenatal smoking and high risk of ADHD inattention symptoms in offspring, but there still remained evidence of an association with high risk of ADHD total and hyperactive-impulsive symptoms (Appendix 5.1). Furthermore, I found evidence of an association between maternal smoking before pregnancy and high risk of hyperactive-impulsive symptoms, but the estimates were stronger with smoking during pregnancy (Appendix 5.2).

Analyses using teacher report of DAWBA and SDQ scales in ALSPAC and TRF in GenR found no strong evidence of an association between maternal smoking during pregnancy and ADHD risk in offspring (Appendix 5.3). In contrast, in GenR I found evidence of an association between maternal smoking during pregnancy and high risk of ADHD total symptoms measured with CBCL (Table 5.6). I did not observe this association for maternal smoking before pregnancy (Appendix 5.4). Results were similar in the analyses with complete cases in each cohort (Appendices 5.5-5.7).

5.3.1.2 Polygenic risk score analyses

In each of the PRS analyses I report the results based on the MR assumptions described in the introduction (see section 5.1).

First, the weighted PRS for smoking heaviness and lifetime smoking were associated with smoking behaviour in pregnancy in ALSPAC and MoBa (all $p<0.01$). These PRS explained 1-3% of variance in smoking phenotypes in ALSPAC and MoBa (Tables 5.8 and 5.9). Associations with unweighted PRS are shown in Appendices 5.8 and 5.9.

Table 5.8. Associations between maternal weighted exposure PRSs and exposure phenotypes in ALSPAC

Exposure	Beta	95% CI	P-value	Sample size	R^2
Smoking heaviness	0.52	0.258, 0.788	0.001	1,537	0.015
Lifetime smoking*	0.67	0.495, 0.837	$4.91x10^{-17}$	7,107	0.010
Lifetime smoking**	9.09	4.521, 18.275	$6.73x10^{-10}$	3,413	0.030
Alcohol consumption	0.29	0.074, 0.501	0.008	3,962	0.019
Coffee consumption	53.45	30.651, 76.252	$4.51x10^{-6}$	7,074	0.004

*Note: *smoking heaviness phenotype; **smoking cessation phenotype (in OR's); 95% CI – 95% confidence intervals; adjusted for principal components; R^2 – variance explained*

Table 5.9. Associations between maternal weighted exposure PRSs and exposure phenotypes in MoBa

Exposure	Beta	95% CI	P-value	Sample size	R^2
Smoking heaviness	0.39	0.112, 0.674	0.006	1,029	0.020
Lifetime smoking*	0.28	0.120, 0.351	$1.05x10^{-12}$	14,488	0.012
Lifetime smoking**	3.21	1.544, 6.660	0.002	3,118	0.027
Alcohol consumption	0.65	-0.757, 2.055	0.365	1,362	NA
Alcohol consumption***	1.06	0.258, 1.859	0.010	12,953	0.007
Coffee consumption	18.80	9.206, 28.402	0.0001	14,583	0.003

*Note: *smoking heaviness phenotype; **smoking cessation phenotype (in OR's); 95% CI – 95% confidence intervals; R^2 – variance explained; ***alcohol consumption before pregnancy; NA – alcohol PRS was not associated with alcohol consumption phenotype; adjusted for birth year, genotyping batch and principal components*

Second, in ALSPAC, I did not find any strong evidence for an association between PRS for smoking heaviness and confounders included in the negative control analyses (Table 5.10). However, in MoBa, I found evidence of an association between the PRS for smoking heaviness and lower parity (β=-0.41, 95%CI -0.732, -0.092; Table 5.11). The PRS for lifetime smoking was associated with younger maternal age (β=-2.64, 95%CI -3.688, -1.586), lower education (β=-1.00, 95%CI -1.286, -0.711), more financial difficulties (β=1.12, 95%CI 0.317, 1.912), higher likelihood of being single (OR=0.24, 95%CI 0.138, 0.415) and having more severe anxiety symptoms (OR=1.98, 95%CI 1.035, 3.801) in ALSPAC (Table 5.12). Similarly, in MoBa, the PRS for lifetime smoking showed evidence of an association with lower maternal education (β=-0.27, 95%CI -0.356, -0.191) and higher likelihood of having more severe depression and anxiety symptoms (OR=1.98, 95%CI 1.052, 3.705; Table 5.13).

Table 5.10. Associations between maternal smoking heaviness PRS and confounders in ALSPAC

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	0.04	-1.437, 1.524	0.954	1,853
Maternal education	Beta	-0.38	-0.782, 0.023	0.065	1,527
Financial difficulties	Beta	0.51	-0.816, 1.826	0.453	1,475
Marital status	OR	1.24	0.662, 2.330	0.500	1,653
Depress. symptoms	OR	0.90	0.395, 2.027	0.791	1,457
Anxiety symptoms	OR	0.99	0.452, 2.162	0.976	1,451
Parity	Beta	0.04	-0.265, 0.341	0.806	1,540

Note: adjusted for principal components; OR- odds ratio; 95% CI – 95% confidence intervals.

Table 5.11. Associations between maternal smoking heaviness PRS and confounders in MoBa

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	-0.21	-13.382, 12.96	0.975	1,125
Maternal education	Beta	-0.12	-0.330, 0.084	0.242	1,069
Financial difficulties	OR	1.10	0.502, 2.416	0.810	966
Marital status	Beta	-0.04	-0.171, 0101	0.611	1,120
Depress. / anxiety symptoms	OR	1.39	0.489, 3.958	0.535	1,112
Maternal ADHD	OR	0.59	0.061, 5.694	0.649	557
Parity	Beta	-0.41	-0.732, -0.092	0.012	1,125

Note: adjusted for birth year, genotyping batch and principal components; OR – odds ratio; 95% CI – 95% confidence intervals.

Table 5.12. Associations between maternal lifetime smoking PRS and confounders in ALSPAC

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	-2.64	-3.688, -1.586	<0.001	7,421
Maternal education	Beta	-1.00	-1.286, -0.711	<0.001	6,860
Financial difficulties	Beta	1.12	0.317, 1.912	0.006	6,691
Marital status	OR	0.24	0.138, 0.415	<0.001	7,124
Depress. symptoms	OR	1.85	0.910, 3.757	0.089	6,706
Anxiety symptoms	OR	1.98	1.035, 3.801	0.039	6,669
Parity	Beta	0.09	-0.111, 0.282	0.392	7,040

Note: adjusted for principal components; OR – odds ratio; 95% CI – 95% confidence intervals.

Table 5.13. Associations between maternal lifetime smoking PRS and confounders in MoBa

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	-0.69	-3.095, 1.723	0.577	14,584
Maternal education	Beta	-0.27	-0.356, -0.191	<0.001	13,836
Financial difficulties	OR	1.57	0.995, 2.477	0.053	13,484
Marital status	Beta	0.01	-0.027, 0.038	0.718	14,519
Depress. / anxiety symptoms	OR	1.98	1.052, 3.705	0.034	14,464
Maternal ADHD	OR	1.90	0.562, 6.403	0.302	8,841
Parity	Beta	0.07	-0.065, 0.200	0.319	14,584

Note: adjusted for birth year, genotyping batch and principal components; OR- odds ratio; 95% CI – 95% confidence intervals.

Third, in ALSPAC, I did not find strong evidence of an association between the PRS for smoking heaviness and high risk of maternal or teacher reported ADHD symptoms in offspring (Table 5.14 and Appendix 5.10). Similarly, in MoBa, I did not find clear evidence of an association between the PRS for smoking heaviness and offspring ADHD risk (Table 5.15). In contrast, I found no clear evidence of an association between the PRS for lifetime smoking and high risk of maternal reported ADHD symptoms in offspring in ALSPAC (Table 5.16), but I did find evidence of an association with high risk of teacher reported ADHD total symptoms measured with both the DAWBA (OR_{DAWBA} = 2.70, 95%CI 1.026, 7.079) and the SDQ (OR_{SDQ} = 3.00, 95%CI 1.034, 8.688; Appendix 5.11.).

There was no strong evidence of an association between maternal PRS for lifetime smoking and high risk of maternal reported ADHD symptoms in MoBa (Table 5.17).

Table 5.14. Associations between maternal smoking heaviness PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	1.04	0.377, 2.885	0.936	1.09	0.389, 3.037	0.873	958
Hyperactive	0.46	0.156, 1.367	0.163	0.45	0.151, 1.362	0.159	959
Inattentive	0.86	0.289, 2.561	0.787	0.89	0.294, 2.680	0.833	958
ADHD (SDQ)	0.12	0.038, 0.403	0.001	0.12	0.037, 0.407	0.001	979

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Table 5.15. Associations between maternal smoking heaviness PRS and high risk of maternal reported offspring ADHD symptoms in MoBa

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (RS-DBD)	1.77	0.423, 7.385	0.435	1.86	0.430, 8.057	0.406	396
Hyperactive	0.80	0.195, 3.282	0.757	0.88	0.211, 3.693	0.865	394
Inattentive	2.82	0.608, 13.097	0.186	3.05	0.639, 14.564	0.162	396

Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components; additionally adjusted for birth year and genotyping batch

Table 5.16. Associations between maternal lifetime smoking PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	0.91	0.421, 1.979	0.818	0.90	0.414, 1.950	0.787	5,005
Hyperactive	0.86	0.380, 1.927	0.706	0.83	0.369, 1.881	0.661	5,016
Inattentive	0.99	0.451, 2.168	0.977	0.98	0.445, 2.142	0.952	5,013
ADHD (SDQ)	1.53	0.641, 3.650	0.338	1.53	0.638, 3.658	0.341	5,103

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Table 5.17. Associations between maternal lifetime smoking PRS and high risk of maternal reported offspring ADHD symptoms in MoBa

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (RS-DBD)	1.02	0.510, 2.036	0.958	1.02	0.510, 2.040	0.957	7,017
Hyperactive	1.02	0.512, 2.021	0.961	1.02	0.513, 2.025	0.957	7,012
Inattentive	1.06	0.510, 2.181	0.885	1.07	0.518, 2.216	0.853	7,017

Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components; additionally adjusted for birth year and genotyping batch

5.3.2 Alcohol

5.3.2.1 Negative control analyses

The pooled estimate of maternal alcohol consumption in the mutually adjusted model showed some evidence of an association with high risk of ADHD total and inattention symptoms (OR_{ADHD}=1.27, 95%CI 1.08, 1.49; OR_{INA}=1.26, 95%CI 1.10, 1.44), but not with high risk of hyperactive-impulsive symptoms (OR_{HYP}=1.13, 95%CI 0.87,1.47). I observed the strongest associations in ALSPAC and MoBa, in GenR the estimates were in opposite direction for high risk of hyperactivity symptoms.

Meta-analysis of paternal alcohol consumption did not show evidence of an association with any of the ADHD symptom domains in offspring (OR_{ADHD}=0.83, 95%CI 0.47, 1.48; OR_{HYP}=0.81, 95%CI 0.53,1.23; OR_{INA}=0.81, 95%CI 0.52,1.27), but there was high heterogeneity and confidence intervals were wide. In ALSPAC, paternal alcohol consumption was negatively associated with ADHD risk in offspring (OR_{ADHD}=0.46, 95%CI 0.31, 0.70; OR_{HYP}=0.53, 95%CI 0.35, 0.82; OR_{INA}=0.52, 95%CI 0.34 to 0.79). This finding was not replicated in GenR and MoBa. The results across unadjusted, adjusted and mutually adjusted models in each cohort are shown in Tables 5.18-5.20.

Table 5.18. Associations between maternal and paternal prenatal alcohol consumption and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (DAWBA)	7,711	1,114			<0.001	6,675	934			0.010	5,384	733			0.002
None (ref)	3,411	450	-	-		2,938	374	-	-		2,369	288	-	-	
<1 unit a week	3,119	455	1.12	0.977,1.293		2,725	389	1.16	0.993,1.362		2,220	311	1.23	1.026,1.471	
>1 unit a week	1,181	209	1.42	1.183,1.693		1,012	171	1.29	1.045,1.586		795	134	1.44	1.128,1.832	
Hyperactive	7,732	982			0.009	6,693	828			0.048	5,394	642			0.009
None (ref)	3,426	407	-	-		2,951	338	-	-		2,378	260	-	-	
<1 unit a week	3,124	398	1.08	0.934,1.255		2,729	346	1.15	0.972,1.350		2,221	272	1.20	0.991,1.443	
>1 unit a week	1,182	177	1.31	1.080,1.580		1,013	144	1.21	0.971,1.507		795	110	1.38	1.064,1.781	
Inattentive	7,723	1,057			0.011	6,688	890			0.061	5,392	708			0.004
None (ref)	3,416	437	-	-		2,943	363	-	-		2,375	279	-	-	
<1 unit a week	3,125	434	1.10	0.953,1.268		2,723	373	1.15	0.980,1.348		2,222	301	1.24	1.031,1.483	
>1 unit a week	1,182	186	1.27	1.057,1.533		1,013	154	1.19	0.964,1.480		795	128	1.41	1.106,1.808	
ADHD (SDQ)	7,983	890			0.003	6,946	737			0.019	5,613	579			0.008
None (ref)	3,521	356	-	-		3,055	291	-	-		2,471	222	-	-	
<1 unit a week	3,225	373	1.16	0.997,1.356		2,837	317	1.23	1.037,1.464		2,310	257	1.32	1.082,1.603	
>1 unit a week	1,237	161	1.33	1.091,1.622		1,054	129	1.27	1.005,1.593		832	100	1.36	1.041,1.781	

									Paternal						
ADHD (DAWBA)	6,049	843			0.019	4,657	622			0.201	4,648	622			0.048
None (ref)	226	49	-	-		148	36	-	-		148	36	-	-	
<1 unit a week	1,404	202	0.61	0.428,0.861		1,054	136	0.49	0.314,0.748		1,053	136	0.45	0.292,0.701	
1-6 units a week	3,164	424	0.56	0.401,0.779		2,471	320	0.53	0.349,0.795		2,465	320	0.47	0.310,0.715	
>1 unit a day	1,255	168	0.56	0.391,0.797		984	130	0.51	0.327,0.787		982	130	0.44	0.279,0.683	
Hyperactive	6,059	735			<0.001	4,666	535			0.018	4,657	535			0.004
None (ref)	226	43	-	-		148	30	-	-		148	30	-	-	
<1 unit a week	1,410	194	0.68	0.471,0.978		1,060	131	0.60	0.383,0.953		1,059	131	0.56	0.350,0.905	
1-6 units a week	3,170	365	0.55	0.390,0.786		2,476	275	0.58	0.374,0.895		2,470	275	0.54	0.343,0.855	
>1 unit a day	1,253	133	0.51	0.346,0.737		982	99	0.50	0.312,0.796		980	99	0.47	0.288,0.771	
Inattentive	6,058	804			0.217	4,666	614			0.359	4,657	614			0.102
None (ref)	227	45	-	-		148	32	-	-		148	32	-	-	
<1 unit a week	1,407	192	0.64	0.446,0.916		1,057	141	0.59	0.379,0.922		1,056	141	0.51	0.320,0.796	
1-6 units a week	3,167	390	0.57	0.403,0.800		2,473	304	0.56	0.367,0.859		2,467	304	0.45	0.291,0.699	
>1 unit a day	1,257	177	0.66	0.461,0.953		988	137	0.62	0.396,0.974		986	137	0.49	0.308,0.781	
ADHD (SDQ)	6,264	669			0.040	4,804	487			0.436	4,796	487			0.156
None (ref)	233	35	-	-		160	24	-	-		160	24	-	-	
<1 unit a week	1,467	172	0.75	0.507,1.113		1,096	114	0.68	0.418,1.110		1,095	114	0.62	0.374,1.027	
1-6 units a week	3,276	327	0.63	0.430,0.915		2,541	245	0.66	0.416,1.061		2,537	245	0.58	0.356,0.941	
>1 unit a day	1,288	135	0.66	0.443,0.989		1,007	104	0.69	0.418,1.127		1,004	104	0.55	0.328,0.928	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's prenatal alcohol consumption*

Table 5.19. Associations between maternal and paternal prenatal alcohol consumption and high risk of maternal and teacher reported offspring ADHD symptoms in GenR

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (CPRS-R)	3,030	440			0.414	1,983	274			0.484	1,532	196			0.581
None (ref)	1,521	210	-	-		920	120	-	-		630	72	-	-	
<1 unit a week	933	145	1.15	0.913,1.445		644	93	1.11	0.809,1.522		507	71	1.25	0.854,1.834	
>1 unit a week	576	85	1.08	0.823,1.419		419	61	1.13	0.781,1.633		395	53	1.12	0.720,1.735	
Hyperactive	3,033	337			0.053	1,987	194			0.198	1,533	144			0.164
None (ref)	1,523	186	-	-		923	98	-	-		631	66	-	-	
<1 unit a week	933	96	0.82	0.635,1.070		644	60	0.84	0.586,1.210		507	44	0.78	0.509,1.207	
>1 unit a week	577	55	0.76	0.551,1.040		420	36	0.76	0.492,1.180		395	34	0.71	0.433,1.169	
Inattentive	3,032	379			0.656	1,988	230			0.698	1,534	170			0.498
None (ref)	1,523	182	-	-		924	100	-	-		632	60	-	-	
<1 unit a week	932	127	1.16	0.912,1.482		644	82	1.19	0.851,1.659		507	62	1.28	0.851,1.913	
>1 unit a week	577	70	1.02	0.758,1.365		420	48	1.05	0.702,1.563		395	48	1.16	0.732,1.842	
ADHD (CBCL)	4,075	585			0.002	2,485	321			0.170	1,828	212			0.105
None (ref)	2,210	347	-	-		1,221	167	-	-		809	101	-	-	
<1 unit a week	1,159	159	0.85	0.697,1.046		769	103	1.04	0.780,1.397		574	67	0.94	0.651,1.356	
>1 unit a week	706	79	0.68	0.521,0.878		495	51	0.73	0.507,1.064		445	44	0.68	0.441,1.062	
ADHD (TRF)	2,970	458			<0.001	1,622	208			0.129	1,148	126			0.178
None (ref)	1,784	333	-	-		849	129	-	-		539	72	-	-	
<1 unit a week	723	76	0.51	0.392,0.668		469	48	0.71	0.480,1.056		342	28	0.60	0.357,1.013	
>1 unit a week	463	49	0.52	0.375,0.710		304	31	0.75	0.466,1.201		267	26	0.72	0.404,1.264	

								Paternal							
ADHD (CPRS-R)	2,373	333			0.266	2,117	289			0.070	1,937	261			0.163
None (ref)	279	28	-	-		221	19	-	-		201	19	-	-	
<1 unit a week	311	54	1.88	1.156,3.070		266	42	2.03	1.107,3.708		238	35	1.58	0.841,2.948	
1-6 units a week	1,166	159	1.42	0.926,2.165		1,069	146	1.85	1.069,3.202		982	133	1.56	0.880,2.746	
>1 unit a day	617	92	1.57	1.003,2.461		561	82	2.06	1.146,3.688		516	74	1.70	0.921,3.139	
Hyperactive	2,373	242			0.901	2,117	202			0.636	1,937	186			0.401
None (ref)	279	26	-	-		221	17	-	-		201	17	-	-	
<1 unit a week	311	42	1.52	0.905,2.551		266	35	1.84	0.962,3.519		238	31	1.68	0.866,3.270	
1-6 units a week	1,166	104	0.95	0.607,1.496		1,069	90	1.17	0.646,2.137		982	83	1.18	0.637,2.185	
>1 unit a day	617	70	1.25	0.775,2.001		561	60	1.50	0.792,2.828		516	55	1.57	0.808,3.045	
Inattentive	2,374	290			0.208	2,119	256			0.111	1,939	234			0.144
None (ref)	279	29	-	-		221	19	-	-		201	18	-	-	
<1 unit a week	311	41	1.31	0.789,2.171		266	36	1.55	0.838,2.884		238	31	1.38	0.719,2.629	
1-6 units a week	1,165	133	1.11	0.727,1.699		1,069	123	1.37	0.788,2.395		982	113	1.28	0.714,2.306	
>1 unit a day	619	87	1.41	0.902,2.203		563	78	1.74	0.963,3.126		518	72	1.63	0.869,3.045	
ADHD (CBCL)	2,898	363			0.320	2,541	305			0.913	2,332	278			0.865
None (ref)	413	52	-	-		319	40	-	-		299	39	-	-	
<1 unit a week	413	66	1.32	0.892,1.954		350	54	1.41	0.885,2.258		317	48	1.38	0.848,2.251	
1-6 units a week	1,376	160	0.91	0.654,1.276		1,244	137	1.02	0.668,1.555		1,139	126	1.09	0.699,1.710	
>1 unit a day	696	85	0.97	0.668,1.396		628	74	1.14	0.710,1.833		577	65	1.17	0.701,1.953	
ADHD (TRF)	1,876	216			0.029	1,570	166			0.829	1,452	149			0.680
None (ref)	325	49	-	-		229	31	-	-		213	28	-	-	
<1 unit a week	261	31	0.76	0.469,1.230		210	19	0.78	0.400,1.536		196	18	0.85	0.411,1.713	
1-6 units a week	865	93	0.68	0.468,0.985		756	79	1.05	0.616,1.779		695	70	1.15	0.643,2.039	
>1 unit a day	425	43	0.63	0.409,0.982		375	37	0.96	0.519,1.789		348	33	1.05	0.534,2.063	

*Note: CPRS-R – Revised Conners' Parent Rating Scale; CBCL – Child Behavior Checklist; TRF – Teacher Report Form; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, parity, parental ethnicity, age, education, anxiety and depression problems, financial difficulties, prenatal smoking and caffeine consumption; **additionally adjusted for partner's alcohol consumption*

Table 5.20. Associations between maternal and paternal prenatal alcohol consumption and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (RS-DBD)	38,134	5,030			<0.001	34,297	4,415			<0.001	10,641	1,395			<0.001
None (ref)	33,605	4,342	-	-		30,216	3,791	-	-		9,800	1,247	-	-	
<1 unit a week	4,366	663	1.21	1.104,1.319		3,931	601	1.33	1.202,1.466		811	146	1.53	1.260,1.865	
>1 unit a week	163	25	1.22	0.795,1.875		150	23	1.12	0.709,1.781		30	2	0.37	0.085,1.647	
Hyperactive	38,127	4,957			<0.001	34,290	4,353			<0.001	10,638	1,351			0.005
None (ref)	33,601	4,281	-	-		30,211	3,741	-	-		9,797	1,214	-	-	
<1 unit a week	4,363	653	1.21	1.102,1.319		3,929	591	1.29	1.166,1.421		811	133	1.40	1.139,1.710	
>1 unit a week	163	23	1.13	0.722,1.754		150	21	1.00	0.625,1.597		30	4	0.89	0.283,2.796	
Inattentive	38,140	4,393			<0.001	34,302	3,874			<0.001	10,639	1,210			0.002
None (ref)	33,610	3,786	-	-		30,220	3,326	-	-		9,799	1,087	-	-	
<1 unit a week	4,367	584	1.22	1.106,1.337		3,932	527	1.31	1.180,1.455		810	120	1.45	1.176,1.793	
>1 unit a week	163	23	1.29	0.833,2.011		150	21	1.20	0.744,1.924		30	3	0.74	0.197,2.777	

								Paternal							
ADHD (RS-DBD)	12,820	1,723			0.594	10,804	1,462			0.807	9,861	1,322			0.366
None (ref)	1,904	255	-	-		613	86	-	-		586	82	-	-	
<1 unit a week	3,405	463	1.02	0.863,1.200		3,192	438	1.00	0.770,1.297		2,945	403	0.97	0.742,1.270	
1-6 units a week	4,684	601	0.95	0.812,1.277		4,360	556	0.89	0.686,1.360		3,971	501	0.85	0.651,1.284	
>1 unit a day	2,827	404	1.08	0.910,1.805		2,639	382	1.04	0.791,1.805		2,359	336	0.97	0.731,1.805	
Hyperactive	12,818	1,684			0.833	10,802	1,432			0.837	9,858	1,294			0.616
None (ref)	1,904	256	-	-		613	89	-	-		586	86	-	-	
<1 unit a week	3,404	452	0.99	0.834,1.164		3,191	421	0.92	0.711,1.182		2,944	387	0.88	0.676,1.137	
1-6 unit a week	4,683	580	0.91	0.776,1.244		4,359	545	0.85	0.656,1.299		3,969	490	0.79	0.611,1.206	
>1 unit a day	2,827	396	1.05	0.884,1.805		2,639	377	1.00	0.765,1.805		2,359	331	0.92	0.698,1.805	
Inattentive	12,821	1,486			0.802	10,806	1,254			0.660	9,862	1,129			0.293
None (ref)	1,903	233	-	-		613	76	-	-		586	72	-	-	
<1 unit a week	3,404	396	0.94	0.793,1.123		3,191	375	0.95	0.726,1.252		2,944	345	0.94	0.708,1.244	
1-6 unit a week	4,686	512	0.88	0.744,1.191		4,362	473	0.84	0.639,1.299		3,972	423	0.81	0.607,1.238	
>1 unit a day	2,828	345	1.00	0.833,1.805		2,640	330	0.98	0.736,1.805		2,360	289	0.92	0.684,1.805	

Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's alcohol consumption*

5.3.2.1.1 Sensitivity analyses

In MoBa, due to the low number of cases, I was not able to report dose-dependent results of the association between maternal alcohol consumption during pregnancy and high risk of maternal reported ADHD symptoms in offspring after adjustment to maternal ADHD (Appendix 5.12). However, maternal alcohol consumption before pregnancy was not associated with high risk of maternal reported offspring's ADHD symptoms (Appendix 5.13). In ALSPAC I found evidence of an association between maternal alcohol consumption before pregnancy and high risk of ADHD symptoms measured with the maternal report of DAWBA but not the SDQ (Appendix 5.14).

Analyses using teacher reported ADHD symptoms in ALSPAC did not find clear evidence of an association with maternal or paternal alcohol consumption during pregnancy measured either with the DAWBA or SDQ (Appendix 5.15). Additionally, the results in ALSPAC and MoBa where I harmonised alcohol units into weekly alcohol consumption in grams did not find clear evidence for associations between maternal alcohol consumption during pregnancy and high risk of maternal reported ADHD symptoms (Appendices 5.16-5.17). The results were similar for the analyses of complete cases in each cohort (Appendices 5.18-5.20).

5.3.2.2 Polygenic risk score analyses

First, in ALSPAC, the PRS for alcohol consumption was associated with alcohol consumption during pregnancy (Table 5.8). However, in Moba, the PRS for alcohol consumption did not predict alcohol consumption during pregnancy (β=-0.65, 95%CI -0.757, 2.055), although it was associated with alcohol consumption before pregnancy (β=1.06, 95%CI 0.258, 1.859) (Table 5.9). The alcohol PRS explained 2% of variance in alcohol phenotype during pregnancy in ALSPAC and 0.7% variance in alcohol phenotype before pregnancy in MoBa.

Associations were similar with unweighted PRS (Appendices 5.8 and 5.9).

Second, the PRS for alcohol consumption was associated with higher maternal education (β=0.52, 95%CI 0.058, 0.983) and with a higher likelihood of having more severe depression symptoms (OR=3.42, 95%CI 1.058, 11.047) in ALSPAC (Table 5.21). However, I found no clear evidence for an association between the PRS for alcohol consumption and confounders in MoBa (Table 5.22).

Table 5.21. Associations between maternal alcohol PRS and confounders in ALSPAC

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	0.46	-1.241, 2.165	0.595	6,944
Maternal education	Beta	0.52	0.058, 0.983	0.027	6,438
Financial difficulties	Beta	1.09	-0.186, 2.368	0.094	6,277
Marital status	OR	0.44	0.182, 1.068	0.070	6,660
Depress. symptoms	OR	3.42	1.058, 11.047	0.040	6,262
Anxiety symptoms	OR	1.85	0.639, 5.362	0.257	6,229
Parity	Beta	0.09	-0.228, 0.401	0.590	6,574

Note: adjusted for principal components; OR – odds ratio; 95% CI – 95% confidence intervals and excluding mothers who did not report drinking before pregnancy

Table 5.22. Associations between maternal alcohol PRS and confounders in MoBa

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	-1.77	-4.678, 1.146	0.235	13,216
Maternal education	Beta	-0.07	-0.199 0.060	0.292	12,524
Financial difficulties	OR	0.83	0.403, 1.049	0.690	12,228
Marital status	Beta	-0.04	-0.097, 0.009	0.102	13,152
Depress. /Anxiety symptoms	OR	0.62	0.230, 1.652	0.336	13,109
Maternal ADHD	OR	2.32	0.327, 16.477	0.400	7,985
Parity	Beta	0.02	-0.188, 0.222	0.870	13,216

Note: adjusted for birth year, genotyping batch and principal components; OR – odds ratio; 95% CI – 95% confidence intervals and excluding mothers who did not report drinking before pregnancy

Third, I found no clear evidence of an association between maternal PRS for alcohol consumption and either high risk of maternal or teacher reported offspring ADHD symptoms in ALSPAC, and with high risk of maternal reported ADHD symptoms in MoBa (Table 5.23-5.24 and Appendix 5.21).

Table 5.23. Associations between maternal alcohol consumption PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	2.01	0.422, 9.542	0.382	2.14	0.449, 10.218	0.339	2,890
Hyperactive	0.46	0.088, 2.429	0.361	0.49	0.094, 2.609	0.406	2,890
Inattentive	1.21	0.249, 5.908	0.811	1.27	0.260, 6.182	0.769	2,893
ADHD (SDQ)	1.53	0.272, 8.566	0.632	1.45	0.259, 8.164	0.671	2,934

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Table 5.24. Associations between maternal alcohol consumption PRS and high risk of maternal reported offspring ADHD symptoms in MoBa

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (RS-DBD)	0.66	0.064, 6.837	0.727	0.64	0.060, 6.769	0.710	1,356
Hyperactive	0.76	0.077, 7.455	0.813	0.83	0.083, 8.374	0.876	1,355
Inattentive	0.95	0.086, 10.479	0.967	0.99	0.089, 11.048	0.993	1,358

Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components; additionally adjusted for birth year and genotyping batch

5.3.3 Caffeine

5.3.3.1 Negative control analyses

The pooled estimate of maternal caffeine consumption in the adjusted model showed some evidence of an association only with high risk of ADHD total symptoms in offspring (OR_{ADHD}=1.05, 95%CI 1.00, 1.11; OR_{HYP}=1.06, 95%CI 0.98, 1.14; OR_{INA}=1.02, 95%CI 0.98, 1.07), whereas the meta-analysis of paternal caffeine consumption in ALSPAC and MoBa did not show associations with ADHD risk in offspring (OR_{ADHD}=1.02, 95%CI 0.97, 1.07; OR_{HYP}=1.00, 95%CI 0.95, 1.06; OR_{INA}=1.03, 95%CI 0.97, 1.09).

I observed stronger associations between maternal caffeine consumption during pregnancy and ADHD risk in MoBa, but not in ALSPAC or GenR (Tables 5.25-5.27).

Table 5.25. Associations between maternal and paternal daily prenatal caffeine consumption and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (DAWBA)	7,680	1,105			<0.001	6,675	934			0.045	5,447	745			0.191
0-49mg (ref)	1,026	119	-	-		895	104	-	-		735	84	-	-	
50-199mg	3,149	435	1.22	0.984,1.517		2,765	369	1.13	0.888,1.432		2,284	304	1.10	0.840,1.429	
200-299mg	1,871	270	1.29	1.021,1.619		1,638	227	1.15	0.891,1.486		1,354	175	1.02	0.767,1.365	
>300mg	1,634	281	1.58	1.257,1.993		1,377	234	1.31	1.008,1.701		1,074	182	1.26	0.937,1.695	
Hyperactive	7,701	978			0.006	6,693	828			0.269	5,458	653			0.381
0-49mg (ref)	1,027	105	-	-		895	93	-	-		735	74	-	-	
50-199mg	3,154	400	1.28	1.016,1.601		2,769	339	1.17	0.909,1.495		2,284	273	1.13	0.853,1.489	
200-299mg	1,878	238	1.27	0.999,1.625		1,644	199	1.13	0.866,1.480		1,359	152	1.02	0.755,1.384	
>300mg	1,642	235	1.47	1.148,1.873		1,385	197	1.22	0.930,1.611		1,080	154	1.22	0.896,1.673	
Inattentive	7,692	1,047			0.268	6,688	890			0.948	5,455	722			0.953
0-49mg (ref)	1,025	132	-	-		895	113	-	-		735	90	-	-	
50-199mg	3,161	424	1.05	0.850,1.292		2,775	363	1.00	0.796,1.266		2,292	302	1.00	0.769,1.293	
200-299mg	1,875	258	1.08	0.862,1.352		1,643	219	1.01	0.786,1.297		1,356	171	0.93	0.701,1.236	
>300mg	1,631	233	1.13	0.896,1.418		1,375	195	0.99	0.763,1.288		1,072	159	1.03	0.769,1.391	
ADHD (SDQ)	7,943	879			0.009	6,946	737			0.710	5,662	586			0.558
0-49mg (ref)	1,047	113	-	-		926	96	-	-		766	77	-	-	
50-199mg	3,228	333	0.95	0.759,1.192		2,847	288	0.95	0.737,1.212		2,349	229	0.91	0.691,1.206	
200-299mg	1,965	204	0.96	0.751,1.221		1,722	166	0.86	0.658,1.132		1,411	127	0.81	0.596,1.100	
>300mg	1,703	229	1.28	1.010,1.632		1,451	187	1.06	0.804,1.390		1,136	153	1.09	0.801,1.486	

									Paternal						
ADHD (DAWBA)	6,124	859			0.325	4,657	622			0.811	4,625	617			0.786
0-49mg (ref)	220	27	-	-		152	18	-	-		151	18	-	-	
50-199mg	773	102	1.09	0.691,1.710		596	77	1.15	0.655,2.008		593	77	1.11	0.634,1.945	
200-299mg	950	135	1.18	0.761,1.842		733	95	1.09	0.631,1.895		729	94	1.02	0.588,1.773	
>300mg	4,181	595	1.19	0.786,1.791		3,176	432	1.13	0.674,1.890		3,152	428	1.03	0.615,1.734	
Hyperactive	6,135	749			0.411	4,666	535			0.719	4,634	533			0.976
0-49mg (ref)	219	24	-	-		151	18	-	-		150	18	-	-	
50-199mg	771	88	1.05	0.649,1.689		596	66	0.97	0.550,1.708		593	66	0.94	0.535,1.663	
200-299mg	953	119	1.16	0.728,1.846		736	76	0.86	0.490,1.498		732	76	0.82	0.469,1.438	
>300mg	4,192	518	1.15	0.742,1.768		3,183	375	0.99	0.592,1.662		3,159	373	0.93	0.554,1.567	
Inattentive	6,133	822			0.784	4,666	614			0.518	4,633	609			0.726
0-49mg (ref)	220	25	-	-		152	14	-	-		151	14	-	-	
50-199mg	777	108	1.26	0.792,2.001		600	78	1.55	0.844,2.860		597	78	1.52	0.827,2.805	
200-299mg	951	127	1.20	0.762,1.897		734	99	1.55	0.850,2.823		730	97	1.46	0.800,2.667	
>300mg	4,185	562	1.21	0.790,1.852		3,180	423	1.52	0.859,2.689		3,155	420	1.44	0.810,2.550	
ADHD (SDQ)	6,323	678			0.346	4,804	487			0.346	4,772	481			0.633
0-49mg (ref)	216	22	-	-		148	12	-	-		147	12	-	-	
50-199mg	790	76	0.94	0.569,1.548		615	58	1.29	0.667,2.490		612	58	1.26	0.650,2.432	
200-299mg	994	108	1.08	0.662,1.744		757	70	1.18	0.619,2.266		753	68	1.09	0.568,2.090	
>300mg	4,323	472	1.08	0.688,1.697		3,284	347	1.34	0.729,2.471		3,260	343	1.23	0.665,2.271	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and alcohol consumption; **additionally adjusted for partner's prenatal caffeine consumption*

Table 5.26. Associations between maternal and paternal daily prenatal caffeine consumption and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (RS-DBD)	42,206	5,607			0.002	34,297	4,415			0.019	12,621	1,686			0.045
0-49mg (ref)	26,564	3,506	-	-		21,616	2,757	-	-		7,844	1,021	-	-	
50-199mg	12,867	1,651	0.97	0.909,1.031		10,462	1,303	0.99	0.922,1.068		4,133	564	1.07	0.957,1.203	
200-299mg	1,869	282	1.17	1.024,1.334		1,497	215	1.14	0.969,1.329		473	66	1.09	0.820,1.435	
>300 mg	906	168	1.50	1.258,1.782		722	140	1.40	1.142,1.723		171	35	1.61	1.073,2.409	
Hyperactive	42,198	5,538			<0.001	34,290	4,353			<0.001	12,620	1,630			<0.001
0-49mg (ref)	26,564	3,386	-	-		21,615	2,644	-	-		7,845	956	-	-	
50-199mg	12,861	1,701	1.04	0.980,1.111		10,456	1,348	1.08	1.004,1.162		4,130	573	1.19	1.058,1.332	
200-299mg	1,868	282	1.22	1.067,1.389		1,497	221	1.21	1.031,1.411		474	65	1.17	0.878,1.550	
>300 mg	905	169	1.57	1.322,1.869		722	140	1.44	1.171,1.760		171	36	1.86	1.250,2.758	
Inattentive	42,215	4,913			0.070	34,302	3,874			0.115	12,620	1,448			0.249
0-49mg (ref)	26,569	3,088	-	-		21,619	2,435	-	-		7,845	888	-	-	
50-199mg	12,872	1,443	0.96	0.898,1.026		10,465	1,135	0.98	0.911,1.064		4,132	474	1.03	0.906,1.159	
200-299mg	1,869	256	1.21	1.051,1.386		1,497	200	1.22	1.038,1.437		473	58	1.09	0.807,1.459	
>300 mg	905	126	1.23	1.014,1.492		721	104	1.15	0.917,1.443		170	28	1.44	0.936,2.198	

								Paternal							
ADHD (RS-DBD)	15,348	2,085			0.365	10,804	1,462			0.535	10,804	1,462			0.710
0-49mg (ref)	3,433	511	-	-		2,353	344	-	-		2,353	344	-	-	
50-199mg	5,527	705	0.84	0.739,0.945		3,861	478	0.85	0.731,0.999		3,861	478	0.84	0.720,0.985	
200-299mg	4,518	609	0.89	0.784,1.012		3,231	448	0.99	0.838,1.157		3,231	448	0.97	0.820,1.136	
>300 mg	1,870	260	0.92	0.786,1.085		1,359	192	1.01	0.824,1.227		1,359	192	0.98	0.804,1.199	
Hyperactive	15,349	2,045			0.189	10,802	1,432			0.929	10,802	1,432			0.729
0-49mg (ref)	3,433	491	-	-		2,352	332	-	-		2,352	332	-	-	
50-199mg	5,530	723	0.90	0.796,1.020		3,862	489	0.91	0.778,1.065		3,862	489	0.89	0.762,1.045	
200-299mg	4,517	582	0.89	0.778,1.009		3,230	428	0.96	0.815,1.132		3,230	428	0.94	0.794,1.104	
>300 mg	1,869	249	0.92	0.781,1.086		1,358	183	0.98	0.798,1.197		1,358	183	0.95	0.775,1.163	
Inattentive	15,350	1,785			0.640	10,806	1,254			0.492	10,806	1,254			0.569
0-49mg (ref)	3,431	437	-	-		2,351	288	-	-		2,351	288	-	-	
50-199mg	5,532	599	0.83	0.729,0.949		3,866	427	0.93	0.785,1.096		3,866	427	0.92	0.777,1.086	
200-299mg	4,517	518	0.89	0.774,1.017		3,230	368	0.97	0.816,1.158		3,230	368	0.96	0.804,1.143	
>300 mg	1,870	231	0.97	0.814,1.145		1,359	171	1.09	0.877,1.342		1,359	171	1.07	0.862,1.322	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, mental health, prenatal smoking and alcohol consumption; **additionally adjusted for partner's caffeine consumption*

Table 5.27. Associations of maternal daily prenatal caffeine consumption on high risk of maternal/teacher reported offspring ADHD symptoms in GenR

	Unadjusted model					Adjusted model*				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (CPRS-R)	2,613	371			0.507	2,053	282			0.438
0-49mg (ref)	499	83	-	-		383	62	-	-	
50-199mg	1,251	169	0.78	0.588,1.042		972	125	0.74	0.520,1.039	
200-299mg	443	55	0.71	0.492,1.026		357	43	0.71	0.456,1.106	
>300mg	420	64	0.90	0.632,1.286		341	52	0.83	0.534,1.297	
Hyperactive	2,617	273			0.236	2,057	201			0.387
0-49mg (ref)	499	65	-	-		383	43	-	-	
50-199mg	1,255	124	0.73	0.532,1.008		976	94	0.85	0.572,1.266	
200-299mg	444	39	0.64	0.423,0.978		358	29	0.74	0.438,1.235	
>300mg	419	45	0.80	0.536,1.204		340	35	0.84	0.500,1.414	
Inattentive	2,616	312			0.770	2,058	240			0.701
0-49mg (ref)	499	70	-	-		383	53	-	-	
50-199mg	1,253	139	0.77	0.562,1.041		976	102	0.69	0.473,0.992	
200-299mg	444	47	0.73	0.489,1.076		358	40	0.77	0.483,1.214	
>300mg	420	56	0.94	0.646,1.376		341	45	0.84	0.526,1.342	
ADHD (CBCL)	3,462	489			0.230	2,565	331			0.285
0-49mg (ref)	688	109	-	-		490	64	-	-	
50-199mg	1,648	232	0.87	0.680,1.114		1,216	155	1.09	0.788,1.516	
200-299mg	591	73	0.75	0.544,1.030		445	54	1.12	0.742,1.690	
>300mg	535	75	0.87	0.630,1.191		414	58	1.26	0.824,1.923	
ADHD (TRF)	2,543	402			0.007	1,671	218			0.128
0-49mg (ref)	565	95	-	-		340	48	-	-	
50-199mg	1,197	208	1.04	0.797,1.358		777	112	1.17	0.791,1.734	
200-299mg	426	60	0.81	0.571,1.152		296	31	0.87	0.513,1.472	
>300mg	355	39	0.61	0.410,0.910		258	27	0.68	0.383,1.200	

*Note: CPRS-R – Revised Conners' Parent Rating Scale; CBCL – Child Behavior Checklist; TRF – Teacher Report Form; N – sample size; n – number of cases; OR - odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, parity, maternal ethnicity, age, education, anxiety and depression symptoms, financial difficulties and prenatal smoking and alcohol consumption*

5.3.3.1.1 Sensitivity analyses

In MoBa, adjustment for maternal ADHD attenuated the association with high risk of ADHD total symptoms but the association with high risk of hyperactive-impulsive symptoms still remained (Appendix 5.22). Furthermore, I also found evidence of an association between maternal caffeine consumption before pregnancy and high risk of offspring's ADHD hyperactive-impulsive symptoms (Appendix 5.23). In ALSPAC and GenR, I found no strong evidence of an association between maternal caffeine consumption during pregnancy and ADHD risk (both maternal and teacher reported ADHD symptoms; Table 5.27 and Appendix 5.24). The results were similar in the analyses with complete cases in each cohort (Appendices 5.25-5.27).

5.3.3.2 Polygenic risk score analyses

First, both the weighted and unweighted PRS for caffeine consumption were associated with total caffeine consumption derived from coffee and tea in ALSPAC and MoBa. The caffeine PRS explained 0.3-0.4% of variance in caffeine phenotype in ALSPAC and MoBa (Tables 5.8 and 5.9 and Appendices 5.8 and 5.9).

Second, I found no clear evidence of an association between the PRS for caffeine consumption and the confounders in ALSPAC and MoBa (Tables 5.28 and 5.29).

Table 5.28. Associations between maternal caffeine PRS and confounders in ALSPAC

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	0.29	-0.406, 0.988	0.412	7,421
Maternal education	Beta	-0.02	-0.211, 0.170	0.832	6,860
Financial difficulties	Beta	0.30	-0.226, 0.829	0.263	6,691
Marital status	OR	0.82	0.569, 1.169	0.267	7,124
Depress. symptoms	OR	0.87	0.540, 1.388	0.550	6,706
Anxiety symptoms	OR	1.14	0.741, 1.756	0.550	6,669
Parity	Beta	-0.02	-0.153, 0.107	0.725	7,040

Note: adjusted for principal components; OR – odds ratio; 95% CI – 95% confidence intervals.

Table 5.29. Associations between maternal caffeine PRS and confounders in MoBa

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	-1.43	-3.101, 0.247	0.095	14,584
Maternal education	Beta	-0.04	-0.094, 0.021	0.213	13,836
Financial difficulties	OR	0.82	0.593, 1.120	0.207	13,484
Marital status	Beta	0.01	-0.009, 0.036	0.236	14,519
Depress /Anxiety symptoms	OR	0.80	0.515, 1.238	0.314	14,464
Maternal ADHD	OR	0.75	0.319, 1.757	0.506	8,841
Parity	Beta	-0.08	-0.174, 0.011	0.083	14,584

Note: adjusted for birth year, genotyping batch and principal components; OR -odds ratio; 95% CI – 95% confidence intervals.

Third, I found no clear evidence of an association between maternal PRS for caffeine consumption and either high risk of maternal or teacher reported offspring's ADHD symptoms in ALSPAC and with high risk of maternal reported ADHD symptoms in MoBa (Tables 5.30 and 5.31 and Appendix 5.28).

Table 5.30. Associations between maternal caffeine consumption PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	0.86	0.513, 1.439	0.564	0.87	0.520, 1.460	0.601	5,005
Hyperactive	0.93	0.540, 1.596	0.787	0.95	0.549, 1.626	0.837	5,016
Inattentive	0.74	0.436, 1.241	0.250	0.74	0.440, 1.255	0.266	5,013
ADHD (SDQ)	1.09	0.615, 1.930	0.769	1.11	0.627, 1.969	0.718	5,103

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Table 5.31. Associations between maternal caffeine consumption PRS and high risk of maternal reported offspring ADHD symptoms in MoBa

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (RS-DBD)	1.16	0.713, 1887	0.549	1.18	0.762, 1.917	0.510	7,017
Hyperactive	1.40	0.863, 2.262	0.174	1.41	0.870, 2.284	0.163	7,012
Inattentive	0.91	0.545, 1.511	0.709	0.91	0.545, 1.512	0.709	7,017

Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components; additionally adjusted for birth year and genotyping batch

5.3.4 Associations between PRS for substance use and participation at age 7-8 years

I found evidence of an association between the PRS for lifetime smoking and lower likelihood of returning the questionnaire at age 7-8 years in ALSPAC and MoBa (OR_{ALSPAC} = 0.49, 95%CI 0.311, 0.757; OR_{MOBA}= 0.59, 95%CI 0.427, 0.801). Furthermore, in MoBa the PRS for smoking heaviness was associated with higher likelihood of returning the questionnaire (OR_{MOBA} = 2.10, 95%CI 1.01, 4.359), but I did not observe a similar association in ALSPAC (OR_{ALSPAC}=0.95, 95% CI 0.561, 1.607) (Tables 5.32 and 5.33).

Table 5.32. Associations between maternal PRSs and participation in ALSPAC

PRS	OR	95%CI	P-value	Sample size
Smoking heaviness	0.95	0.561, 1.607	0.848	2,345
Lifetime smoking	0.49	0.311, 0.757	0.001	7,915
Alcohol consumption	0.98	0.398, 2.403	0.961	4,789
Caffeine consumption	1.28	0.951, 1.714	0.105	7,915

Note: OR – odds ratio; 95% CI – 95% confidence intervals; adjusted for principal components

Table 5.33. Associations between maternal PRSs and participation in MoBa

PRS	OR	95%CI	P-value	Sample size
Smoking heaviness	2.10	1.01, 4.359	0.047	1,125
Lifetime smoking	0.59	0.427, 0.801	0.001	14,584
Alcohol consumption	0.74	0.237, 2.314	0.605	2,861
Caffeine consumption	1.07	0.856, 1.324	0.575	14,584

Note: OR – odds ratio; 95% CI – 95% confidence intervals; adjusted for principal components, genotyping batch and birth year

5.4 DISCUSSION

In this study I investigated whether maternal smoking, alcohol and caffeine use during pregnancy are likely to be causally associated with ADHD risk in offspring. I triangulated findings using negative control and polygenic risk score analyses and compared results across three longitudinal birth cohorts.

Overall, my negative control and PRS analyses did not provide strong evidence for a potential causal effect of maternal smoking, alcohol or caffeine consumption during pregnancy on ADHD risk in offspring although I observed some inconsistencies across the cohorts and questionnaire used for ADHD assessment.

My results on smoking did not show strong evidence for a causal effect, which is in line with previous findings (Gustavson et al., 2017; Langley et al., 2012; Roza et al., 2009). Although in GenR and MoBa, I found suggestive evidence for a causal effect of maternal smoking during pregnancy on high risk of maternal reported ADHD total symptoms, when comparing the findings across the cohorts, reporters and questionnaires, the evidence was weak and inconsistent. Additionally, my PRS analyses with lifetime smoking PRS in ALSPAC and MoBa indicated pleiotropic associations which are consistent with my findings in Chapter 4. This is also consistent with the large body of evidence showing pleiotropy between smoking PRS, impulsivity and sensation-seeking type of personality (Harrison et al., 2020; Khouja et al., 2021), which could have confounded observed associations in this study.

Similarly, my findings on alcohol exposure do not show evidence of a causal effect on ADHD risk in offspring. Although a previous study in MoBa found weak evidence for a potential causal effect of maternal alcohol consumption during pregnancy when ADHD symptoms were measured with CPRS-R (Eilertsen et al., 2017), other studies using alternative analytical approaches more similar to the present one suggested that observed

associations between maternal moderate alcohol consumption during pregnancy and ADHD symptoms in offspring may not be causal (D'Onofrio et al., 2007; Lund et al., 2019).

My results on caffeine exposure are in line with previous studies which have also concluded no causal effect of caffeine consumption during pregnancy on ADHD symptoms in offspring (Del-Ponte et al., 2016; Loomans et al., 2012). However, previous studies in MoBa have found an association between maternal prenatal caffeine intake from soft drinks and higher risk for overactivity in 18 months old children (Bekkhus et al., 2010; Berglundh et al., 2020). Although a study by Berglundh and colleagues further reported that there was no difference in this association between caffeinated and non-caffeinated soft drinks and no associations were observed between caffeine intake from different sources of caffeine with offspring ADHD symptoms at age 8 years. The same study also showed that smokers and participants with lower education drank soft drinks more often and therefore the association observed with overactivity in their study and associations observed in my study are likely to be confounded.

Several studies have reported low to moderate parent-teacher agreement on ADHD symptoms assessment (Narad et al., 2015; Sollie et al., 2013). It has been suggested that parents and teachers may measure different aspects of child's behaviour as ADHD symptoms may be more visible at school which is a more structured environment (Narad et al., 2015). Furthermore, it has been also proposed that parent-teacher ratings may differ because of the informant's perception and individual characteristics (Amador-Campos et al., 2006). For example, it has been shown that mothers with mental health problems and more harsh parenting behaviour overestimate their child's mental health problems (Lavigne et al., 2015; Najman et al., 2001). Given that I observed more associations with maternal report than with teacher report, it is possible that observed associations may be confounded by maternal characteristics.

Besides reporter-related discrepancies, I also observed different findings depending on the scales used for ADHD assessment. Previous studies investigating the association between maternal substance use during pregnancy and ADHD in offspring have reported inconsistent findings depending on which scale was used for ADHD assessment. For example, a study using the SDQ scale reported association between maternal smoking during pregnancy and ADHD symptoms in children regardless of the reporter (Sutin et al., 2017). Another study using maternal and teacher reported CPRS-R, as well as CBCL, TRF and combined score of CBCL/TRF found some evidence for an association between maternal smoking during pregnancy and maternal reported CPRS-R indicating potential causal effect and suggesting that this is a more sensitive measure for assessing ADHD symptoms (Knopik et al., 2016). Similarly, a study on prenatal alcohol exposure found some evidence for a causal effect when ADHD symptoms were assessed with maternal reported CPRS-R but not with CBCL (Eilertsen et al., 2017).

Although all the scales for the main outcome measure (DAWBA, CPRS-R, RS-DBD) are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD, I observed inconsistent associations between maternal prenatal substance use and high risk of ADHD symptoms across different scales. More research is needed to better understand if these different scales capture the same construct of ADHD symptoms. In addition, the observed and unobserved associations could be also affected by dichotomised outcome measures as dichotomising influences statistical power.

Considering that previous studies have reported inconsistent results, the major strength of this study is the triangulation approach using both observational and genetic analyses. Further, using data from three longitudinal birth cohorts and comparing results across the cohorts helps to strengthen evidence towards causal inference. If results are consistent across the cohorts, this would give stronger support for or against a causal effect.

However, this study has also several limitations. First, outcome assessment varied across the cohorts and although all the questionnaires have good psychometric properties, there may still be a risk of measurement error. Moreover, dichotomized covariates (such as maternal ADHD symptoms in MoBa) may be affected by residual confounding. Second, maternal substance use during pregnancy was based on self-reports. Given the stigmatization of prenatal substance use, mothers may have underreported their prenatal substance use which can affect observed results. Third, I calculated PRS for smoking heaviness and alcohol consumption based on summary statistics from the latest GWAS which included ALSPAC. However, the contribution of ALSPAC sample (~1%) was small and the risk of bias because of the sample overlap is likely to be minimal (Burgess et al., 2016). Fourth, my PRS analyses were likely underpowered. Compared to the variance explained by each PRS reported in GWAS (smoking heaviness PRS ~4%; alcohol PRS ~2.5%; caffeine PRS 1.3%), in my sample it was much smaller. Fifth, the sample size in adjusted models were reduced due to missing data in the included confounders which could introduce bias into the estimates. However, I performed all analyses restricting to individuals in the mutually adjusted models and effect estimates remained consistent.

Sixth, several studies have reported that longitudinal cohort studies may suffer from selection bias as socioeconomic and individual characteristics may affect initial and continued participation in the study (Launes et al., 2014; Nohr et al., 2006). A study in MoBa found that bias due to self-selection and loss to follow-up can influence exposure-outcome associations (Biele et al., 2019). Furthermore, a study in ALSPAC also showed that common genetic variants of various phenotypes are associated with participation in the study and these associations differ in the sample with full genetic data and more selected subsamples (Taylor, Jones, et al., 2018). Given that attrition in this study sample was more than 50% and I also observed association between PRS for lifetime smoking and decreased likelihood returning the questionnaire at child's age 7-8 years, it is plausible that these results may be subject to selection bias.

5.5 CHAPTER SUMMARY

In this chapter I combined both observational and genetic analyses using data from three longitudinal birth cohorts. I did not find strong support for a causal effect of maternal smoking, alcohol or caffeine consumption during pregnancy on ADHD risk in offspring. However, I observed somewhat different findings between maternal and teacher reported ADHD symptoms, as well as between the scales used for ADHD assessment.
In the next chapter I will focus more on alcohol exposure by using genetic variants from alcohol metabolising genes as a proxy for fetal alcohol exposure.

Chapter 6 MATERNAL AND OFFSPRING POLYGENIC RISK SCORE (PRS) ANALYSES OF FETAL ALCOHOL EXPOSURE AND ADHD RISK IN OFFSPRING

This chapter is based on the manuscript "Maternal and offspring genetic risk score (GRS) analyses of fetal alcohol exposure and ADHD risk in offspring." Preprint of this manuscript is available in medRxiv https://doi.org/10.1101/2021.03.30.21254492

While Chapter 5 examined all three prenatal substance use exposures, this chapter focuses exclusively on prenatal alcohol exposure. In Chapter 5 alcohol exposure was proxied by SNPs based on GWAS summary statistics of alcohol consumption per week and I did not find clear evidence for a causal effect. In this chapter I take a different approach, using genetic variants in both maternal and fetal alcohol metabolising genes as proxies for fetal alcohol exposure. This choice acknowledges that fetal blood alcohol levels may depend on maternal and fetal ability to metabolise alcohol, and not just maternal alcohol use. Thus, I investigated further whether fetal alcohol exposure is causally associated with high risk of offspring total ADHD symptoms, as well as separately with hyperactive-impulsive and inattention symptoms.

6.1 INTRODUCTION

It is well documented that alcohol consumption during pregnancy negatively affects fetal development. The harmful neurodevelopmental effects resulting from prenatal alcohol exposure (PAE) are collectively defined as fetal alcohol spectrum disorders (FASD) (Mattson et al., 2019). However, as described in Chapter 1 (see section 1.4.3 "Burden of maternal prenatal substance use") there is a substantial overlap between FASD, ADHD and other behavioural impairment (Lange et al., 2019; Popova et al., 2016; Weyrauch et al., 2017), and a lack of clear diagnostic criteria of FASD makes it difficult to distinguish FASD from other neurodevelopmental

disorders (Burd, 2016). Although ADHD is one of the most common neurodevelopmental disorder diagnoses in FASD, little is known about the role of PAE in causing ADHD risk specifically in the general population.

Furthermore, the risks of heavier PAE on children's health outcomes – including neurodevelopmental problems – are clear, but evidence is still inconsistent regarding the effects of low PAE (Mamluk et al., 2017). A systematic review by Easey and colleagues suggested that low and moderate alcohol consumption during pregnancy is associated with negative mental health outcomes in children, including anxiety/depression, total behavioural problems and conduct disorder (Easey, Dyer, et al., 2019). However, another recent systematic review and meta-analysis focusing specifically on offspring ADHD found little evidence to suggest an increased risk of ADHD symptoms in children whose mothers consumed moderate amounts of alcohol (up to 70 grams a week) during pregnancy (Porter et al., 2019). In contrast, low PAE was found to have a protective effect on ADHD symptoms in some earlier studies (Kelly et al., 2013; Niclasen et al., 2014). However, it is possible that these associations are due to genetic confounding or confounding by social factors, as both studies found that women who drank low or moderate levels during pregnancy had a higher socio-economic position.

As discussed in previous chapters (Chapter 4 and 5) studies using conventional observational designs may be biased due to unmeasured and residual confounding (Davey Smith and Ebrahim, 2003). One potential approach to overcome these limitations is to use genetic variants predictive of alcohol consumption or directly involved in alcohol metabolism to disentangle effects of PAE on child outcomes. Mendelian Randomization (MR) approach, as explained in Chapter 5 offers another useful perspective to evaluate the strength of evidence for a causal relationship, as the genetic variants used as a proxy for the exposure are generally less affected by confounding factors than the self-reported exposure measurements used in more conventional epidemiological analyses (Davey Smith and Hemani, 2014). Nevertheless, if evidence is consistent across different methods, this

provides stronger support for a causal influence of the exposure (prenatal alcohol consumption) on the outcome (offspring ADHD) (Davey Smith and Ebrahim, 2003).

In Chapter 5, I derived the alcohol PRS using SNPs identified from the latest GWAS on alcohol consumption per week (Liu et al., 2019). However, the alcohol PRS was based on a discovery sample of general population individuals, who on average consume more alcohol than pregnant women. Therefore, studies examining prenatal exposures may be affected by lower power to detect an effect. Moreover, there is evidence that harmful effects of alcohol exposure are also affected by maternal and fetal metabolic capacity which can lead to different fetal alcohol levels if pregnant women drink during pregnancy (Burd et al., 2012). Therefore, analyses based on the PRS of alcohol consumption per week could miss biologically important effects related to individual differences in the ability to metabolise alcohol.

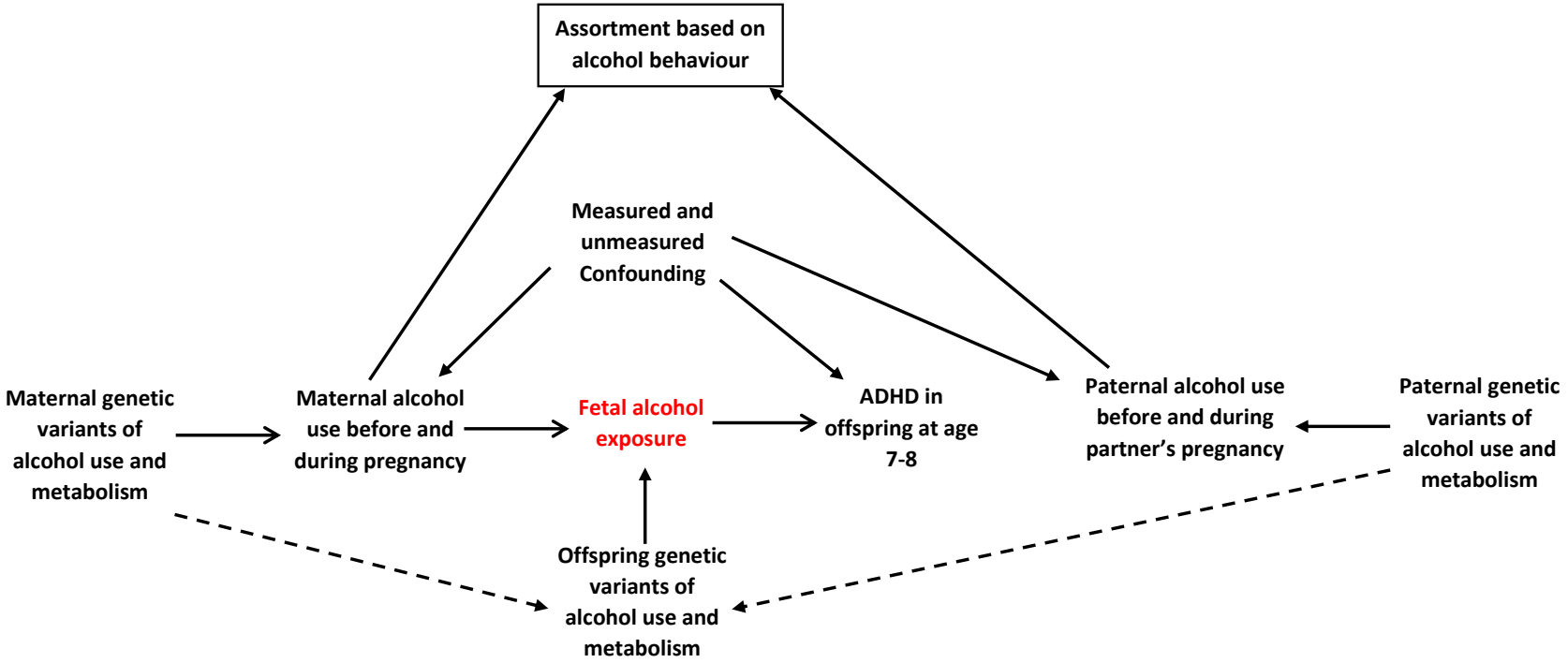
A large body of research has shown that ethanol metabolism is affected by a group of alcohol dehydrogenase (*ADH: ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7*) and aldehyde dehydrogenase (*ALDH: ALDH1A1 and ALDH2*) genes, and variants in these genes have an impact on how quickly alcohol is metabolised, the amount of alcohol consumed and individual effects of alcohol consumption (Birley et al., 2009; Birley et al., 2008; Edenberg and McClintick, 2018). The majority of *ADH* genes are expressed in the liver with the exception of *ADH7* which is expressed in the stomach (Edenberg and McClintick, 2018). It has been reported that more than 90% of ethanol is metabolised through the liver (Pizon et al., 2007).

Of relevance to this study of intrauterine effects, genetic variants in some *ADH* genes are also expressed in early fetal development. After maternal alcohol intake, fetal blood alcohol concentration is nearly equivalent to maternal alcohol levels (Burd et al., 2012) and although the fetus is able to metabolise some alcohol, the majority of alcohol metabolism acts through maternal metabolic pathways (Burd et al., 2012). Therefore, it is possible that the severity of effects of fetal alcohol exposure on offspring health

outcomes depends on both fetal and maternal metabolic activity. The importance of fetal *ADH* genetic variants is evidenced by previous studies using the ALSPAC sample which have shown that four child *ADH* genetic variants were associated with lower IQ at age 8 and early onset conduct problems in children whose mothers drank during pregnancy (Lewis et al., 2012; Murray et al., 2016). However, these studies used a PRS comprised of four *ADH* genetic variants, and it is still unknown how these four genetic variants change metabolic activity.

It remains unclear whether PAE has a causal effect on ADHD risk in offspring, through modulations of maternal and fetal alcohol metabolism. In this study, I use genetic variants in *ADH/ALDH* genes as proxies for fetal alcohol exposure and investigate their association with high risk of offspring ADHD symptoms, as well as separately with hyperactive-impulsive and inattention symptom domains. An overview of the study design is shown in Figure 6.1.

Figure 6.1. Study design



Note: Maternal and offspring genetic variants of alcohol use and metabolism were used as proxies for fetal alcohol exposure (the exposure of interest, unmeasured) to investigate associations with ADHD risk in offspring around age 7-8 years (outcome). Dashed arrows represent genetic correlation as a child inherits 50% of its genetic make-up from mother and father. In this study I assume that mate selection is not based on confounders but could be affected by alcohol behaviour. Adjustment to paternal genetic data will help to overcome potential bias because of the assortment and shared genetics.

6.2 METHODS

6.2.1 Study Populations

Similarly to Chapter 5, I used data from three European prospective longitudinal birth cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC), the Generation R (GenR) and the Norwegian Mother, Father and Child Cohort Study (MoBa). More details about each cohort are given in Chapter 3 (see sections 3.2.1; 3.3.1 and 3.4.1)

6.2.2 Availability of genome-wide data

In ALSPAC, genome-wide data are available for 8,237 children and 8,196 mothers. In GenR, genetic data are available for 5,732 children, but maternal genetic data was not available at the time of analyses. In MoBa, genetic data are currently available for 14,112 children, 13,614 mothers and 13,935 fathers. Detailed information about the genotyping in the ALSPAC and MoBa cohorts is presented in Chapter 3 (see sections 3.2.2 and 3.4.2).

6.2.3 Exposures

More details about exposure assessment in each cohort is given in Chapter 3 (see sections 3.2.4; 3.3.4 and 3.4.4).

Compared to Chapter 5, in this study I used a cumulative measure of alcohol consumption throughout pregnancy and mothers who reported alcohol consumption at any point during the pregnancy were classified as drinkers.

6.2.3.1 Genetic variants

I identified genes responsible for alcohol metabolism expressed in liver and brain in mothers and fetus using Expression Atlas (Kapushesky et al., 2010; Papatheodorou et al., 2020), as this online tool provides information about biological underpinning. More specifically, Expression Atlas is a database

which provides information about gene expression across different species (incl. humans), tissues, cells, as well as about experimental conditions and diseases (Papatheodorou et al., 2020). Using this online tool, I identified *ADH1A, ADH1B, ADH4, ADH5, ADH6, ALDH2, ALDH1A1 and ALDH1B1* that were expressed in adults and fetus, and additionally *ADH1C* and *ADH7* genes which were only expressed in adults. All these genes are located in chromosomes 4, 9 and 12. In total I identified 869 single nucleotide polymorphisms (SNPs) from these genes available in the genome-wide dataset from ALSPAC (shown in Appendices 6.1-6.3). Given the high linkage disequilibrium of these SNPs, I used a clumping procedure with a R^2 threshold of 0.01 to identify independent SNPs. A clumping procedure was preferred over the pruning method as clumping identifies independent SNPs by using an SNP with the lowest p-value as an index SNP, and can retain multiple SNPs in the same genomic region, whereas pruning selects independent SNPs based on correlations between the SNP pairs which may leave genomic region without representative SNP (Choi et al., 2020; Purcell et al., 2007).

I used 1000 Genomes as a reference panel for clumping, which was also used for genetic imputation in ALSPAC. After clumping, I identified 36 independent SNPs, these are listed in Table 6.1. Although there is evidence that the genetic variant rs1229984 from *ADH1B* gene has a functional role in alcohol metabolism (Zuccolo et al., 2009), this SNP was not included in my list after clumping. However, my list included an SNP rs141973904 which was correlated with an SNP rs1229984 (r=0.55).

Table 6.1. Independent SNPs identified after clumping

SNP	Chromosome
rs7669660	4
rs116010022	4
rs28730582	4
rs29001207	4
rs13125262	4
rs17033	4
rs138331988	4
rs17028839	4
rs138244919	4
rs141973904	4
rs3805329	4
rs75756595	4
rs1154465	4
rs4646769	9
rs77054814	9
rs12378961	9
rs10973779	9
rs8187999	9
rs8187996	9
rs168351	9
rs8187953	9
rs8187950	9
rs78094588	9
rs8187928	9
rs34878833	9
rs8187898	9
rs80105873	9
rs8187891	9
rs17648566	9
rs116917518	9
rs11143426	9
rs41287405	9
rs148620777	12
rs2283354	12
rs73205605	12
rs61941278	12

6.2.4 Outcome

In this study I used the same outcome measures as in Chapter 5. More details about the questionnaires used in ADHD assessment in each cohort are provided in Chapter 3 (see sections 3.2.3.1 and 3.2.3.2; 3.3.3.1 and 3.3.3.2; and 3.4.3.1).

The psychometric scales used for the primary outcome measure assessed at age 7-8 years were: maternal report of the Development And Well-Being Assessment (DAWBA) questionnaire in ALSPAC; maternal report of the

revised Conner's Parent Rating Scale (CPRS-R) in GenR; and maternal report of the Rating Scale for Disruptive Behavior Disorders (RS-DBD) in MoBa.

The secondary outcome measures were: teacher report of the DAWBA questionnaire and maternal and teacher report of the Strengths and Difficulties Questionnaire (SDQ) hyperactivity subscale in ALSPAC and maternal and teacher report of the Child Behavior Checklist (CBCL) attention problems subscale in GenR.

6.2.5 Harmonisation

Before calculating PRS, I conducted harmonisation to ensure that alleles were coded on the same DNA strand (in a positive 5' to 3' strand) to reduce potential issues with palindromic variants. Genetic variants are called palindromic if they are the same in both DNA strands (such as SNPs with A/T or G/C alleles) (Anjana et al., 2013). Harmonisation of palindromic variants can be problematic if allele frequencies are close to 0.5 as it would be difficult to identify which of the alleles is the effect allele in the exposure and the outcome GWAS (Hartwig et al., 2016). Harmonisation is essential in genetic association studies when multiple independently generated datasets are used (Hartwig et al., 2016).

In addition, I also aligned the SNPs so that the effect alleles were all positively associated with alcohol consumption in the discovery sample. These effect estimates were taken from the summary statistics of the latest GWAS on alcohol consumption per week (GSCAN) (Liu et al., 2019). If effect alleles in GSCAN were negatively associated with the exposure, then effect alleles in the discovery sample were flipped to the other allele to ensure that all variants are in the exposure-increasing direction.

The harmonisation procedure in ALSPAC is shown in Table 6.2. All the SNPs identified in ALSPAC were also available in GenR and I aligned the SNPs similarly as in ALSPAC (Appendix 6.4). However, in MoBa genetic imputation was conducted using the Haplotype Reference Consortium (HRC) as a genetic reference panel, and 9 SNPs identified in ALSPAC were unavailable

in MoBa. I identified proxy for these SNPs using Single Nucleotide Polymorphisms Annotator (SNiPA) (Arnold et al., 2015) and also aligned these SNPs based on the summary statistics of the latest GWAS on alcohol consumption per week (Table 6.3).

Table 6.2. Harmonisation of SNPs in ALSPAC based on the GSCAN summary statistics

GSCAN					ALSPAC			
SNP	**Non-effect allele**	**Effect allele**	**Effect allele frequency**	**Beta**	**Minor allele**	**Major allele**	**Minor allele frequency**	**Effect allele after harmonisation**
rs7669660	T	C	0.136	0.0086	C	T	0.1481	C
rs116010022	C	A	0.00942	-0.0023	A	C	0.0131	C
rs28730582	C	T	0.0318	0.0149	T	C	0.0294	T
rs29001207	G	C	0.038	-0.0334	C	G	0.0512	G
rs13125262	G	C	0.0436	0.0160	C	G	0.0498	C
rs17033	T	C	0.0881	-0.0063	C	T	0.0880	T
rs138331988	G	A	0.0192	0.0042	A	G	0.0180	A
rs17028839	A	G	0.039	0.0031	G	A	0.0437	G
rs138244919	C	T	0.0272	0.0052	T	C	0.0258	T
rs141973904	C	T	0.0178	-0.1990	T	C	0.0120	C
rs3805329	T	C	0.0625	0.0105	C	T	0.0650	C
rs75756595	G	A	0.0522	0.0015	A	G	0.0499	A
rs1154465	T	A	0.0276	0.0061	A	T	0.0248	A
rs4646769	T	C	0.857	-0.0014	T	C	0.1372	T
rs77054814	A	G	0.067	0.0017	G	A	0.0612	G
rs12378961	C	G	0.0573	0.0068	G	C	0.0705	G
rs10973779	G	A	0.0299	-0.0067	A	G	0.0312	G
rs8187999	C	G	0.0238	0.0111	G	C	0.0265	G
rs8187996	C	T	0.0479	-0.0030	T	C	0.0502	C
rs168351	A	G	0.147	-0.0039	G	A	0.1564	A
rs8187953	C	G	0.0268	0.0011	G	C	0.0308	G
rs8187950	A	G	0.0364	-0.0033	G	A	0.0366	A
rs78094588	G	A	0.0233	0.0031	A	G	0.0178	A
rs8187928	C	T	0.0253	0.0103	T	C	0.0212	T
rs34878833	G	A	0.0231	0.0139	A	G	0.0348	A
rs8187898	T	C	0.0259	0.0038	C	T	0.0288	C

rs80105873	G	T	0.0289	-0.0029	T	G	0.0337	G
rs8187891	T	C	0.0252	0.0002	C	T	0.0268	C
rs17648566	T	C	0.0204	-0.0093	C	T	0.0205	T
rs116917518	A	T	0.0351	-0.0020	T	A	0.0512	A
rs11143426	A	G	0.0127	0.0147	G	A	0.0150	G
rs41287405	T	C	0.0238	0.0057	C	T	0.0283	C
rs148620777	A	G	0.0177	-0.0048	G	A	0.0177	A
rs2283354	G	A	0.174	0.0023	A	G	0.1742	A
rs73205605	G	A	0.036	-0.0018	A	G	0.0442	G
rs61941278	A	G	0.013	0.0075	G	A	0.0260	G

Note: GWAS & Sequencing Consortium of Alcohol and Nicotine use

Table 6.3. Harmonisation of SNPs in MoBa based on the GSCAN summary statistics

	GSCAN					MoBa			
SNP	**New proxy SNP**	**Non-effect allele**	**Effect allele**	**Effect allele frequency**	**Beta**	**Reference allele**	**Alternate allele**	**Reference allele frequency**	**Effect allele after harmonisation**
rs7669660		T	C	0.136	0.0086	T	C	0.1364	C
rs116010022	rs11724783	C	A	0.425	0.0003	C	A	0.4252	A
rs28730582		C	T	0.0318	0.0149	C	T	0.0318	T
rs29001207		G	C	0.038	-0.0334	G	C	0.0380	G
rs13125262	rs13133633	C	G	0.272	0.0061	C	G	0.2717	G
rs17033		T	C	0.0881	-0.0063	T	C	0.0881	T
rs138331988		G	A	0.0192	0.0042	G	A	0.0192	A
rs17028839		A	G	0.039	0.0031	A	G	0.0390	G
rs138244919		C	T	0.0272	0.0052	C	T	0.0272	T
rs141973904	rs143502255	C	T	0.366	-0.0023	C	T	0.3658	C
rs3805329		T	C	0.0625	0.0105	T	C	0.0625	C
rs75756595		G	A	0.0522	0.0015	G	A	0.0522	A
rs1154465		T	A	0.0276	0.0061	T	A	0.0276	A
rs4646769		T	C	0.857	-0.0014	T	C	0.8574	T
rs77054814		A	G	0.067	0.0017	A	G	0.0670	G
rs12378961		C	G	0.0573	0.0068	C	G	0.0573	G
rs10973779		G	A	0.0299	-0.0067	G	A	0.0299	G
rs8187999		C	G	0.0238	0.0111	C	G	0.0238	G
rs8187996		C	T	0.0479	-0.0030	C	T	0.0479	C
rs168351		A	G	0.147	-0.0039	A	G	0.1467	A
rs8187953	rs918836	G	C	0.312	0.0002	G	C	0.3116	C
rs8187950	rs8187924	G	A	0.501	-0.0010	G	A	0.5008	G
rs78094588		G	A	0.0233	0.0031	G	A	0.0233	A
rs8187928		C	T	0.0253	0.0103	C	T	0.0253	T
rs34878833		G	A	0.0231	0.0139	G	A	0.0231	A
rs8187898		T	C	0.0259	0.0038	T	C	0.0259	C

rs80105873	rs7848927	G	T	0.559	-0.0004	G	T	0.5588	G
rs8187891		T	C	0.0252	0.0002	T	C	0.0252	C
rs17648566	rs7860944	C	T	0.604	-0.0026	C	T	0.6040	C
rs116917518		A	T	0.0351	-0.0020	A	T	0.0351	A
rs11143426		A	G	0.0127	0.0147	A	G	0.0127	G
rs41287405	rs4237253	C	T	0.5	-0.0010	C	T	0.4995	C
rs148620777		A	G	0.0177	-0.0048	A	G	0.0177	A
rs2283354		G	A	0.174	0.0023	G	A	0.1738	A
rs73205605		G	A	0.036	-0.0018	G	A	0.0360	G
rs61941278	rs61941274	G	A	0.0148	0.0073	G	A	0.0148	A

Note: GWAS & Sequencing Consortium of Alcohol and Nicotine use

6.2.6 Polygenic risk scores

As it is not possible to directly measure the effect of each SNP on fetal exposure to alcohol, and therefore to calculate weights, I derived unweighted PRS using 36 independent SNPs (Table 6.1). Similarly to Chapter 5, I calculated a sum score of SNPs using PLINK v1.90 (Purcell et al., 2007) for offspring in all the cohorts, for mothers in ALSPAC and MoBa and additionally for fathers in MoBa.

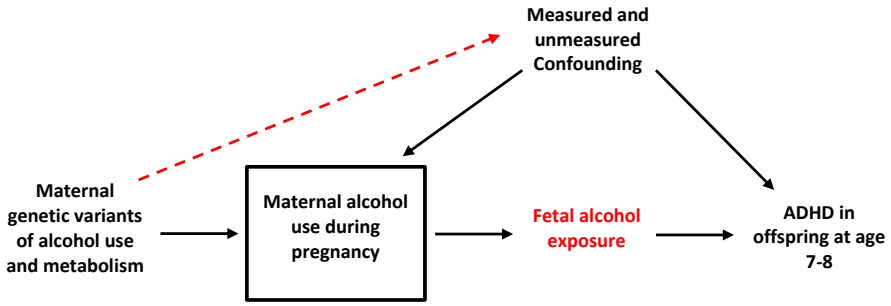
6.2.7 Statistical analysis

I performed all analyses using Stata v15 in ALSPAC and GenR and Stata v16 in MoBa (StataCorp, 2017, 2019) and restricted to unrelated individuals and additionally to European ancestry in GenR (sample size 2,661 children). Before I performed the analyses, I submitted the pre-registered protocol to the Open Science Framework (https://doi.org/10.17605/OSF.IO/AQRXP).
I tested associations between maternal and offspring PRS and ADHD risk in offspring using logistic regression. I adjusted all analyses for 10 ancestry informed principal components and in MoBa additionally for birth year and genotyping batch.

6.2.7.1 Primary analysis

I performed analyses using three models: 1) maternal PRS; 2) maternal PRS adjusted for offspring PRS; 3) maternal PRS adjusted for offspring and paternal PRS. I performed these analyses in the full sample without stratifying based on maternal drinking status, because this could induce collider bias thus introducing a spurious association between the PRS and confounders (Figure 6.2).

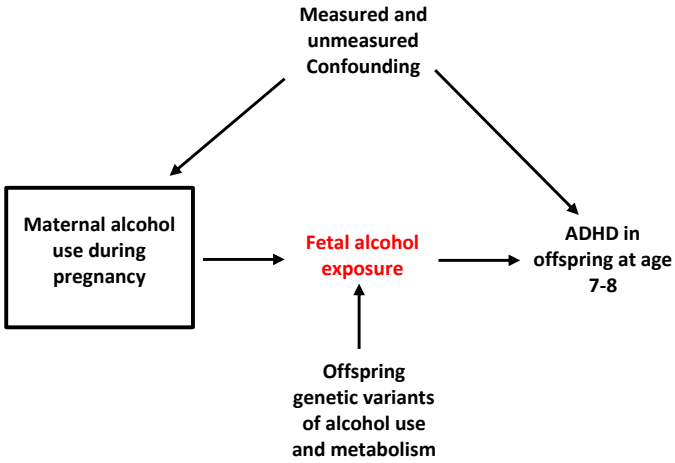
Figure 6.2. Collider bias in maternal PRS analyses



Note: Conditioning on maternal drinking status during pregnancy induces a form of bias known as collider bias. In practice, this manifests as an artefactual association (red dashed arrow) between genetic variants of alcohol use and confounders. This may induce a spurious association between the exposure and outcome as genetic propensities in women who drink may differ from women who abstain.

Similarly, I used three models for the offspring PRS analyses too: 1) offspring PRS; 2) offspring PRS adjusted for maternal PRS; 3) offspring PRS adjusted for maternal and paternal PRS. This time, I stratified these analyses by maternal drinking status during pregnancy, since fetal alcohol exposure cannot affect maternal prenatal alcohol consumption and collider bias could not be an issue as in the case of maternal PRS analyses (Figure 6.3).

Figure 6.3. Collider bias in offspring PRS analyses



Note: Conditioning on maternal drinking status during pregnancy in offspring PRS analyses does not induce collider bias as offspring genetic variants does not affect maternal alcohol use. However, adjustment for maternal PRS is still necessary given the shared genetics between child and mother.

As in Chapter 5, I performed analyses separately in each cohort and then meta-analysed across the cohorts using a random effects model which takes into account variability in the exposure and outcome assessment across the cohorts. ALSPAC and MoBa results from model 2 (maternal PRS adjusted for offspring PRS) were pooled in meta-analyses, while all three cohorts contributed to meta-analyses for model 1 (offspring PRS) results.

6.2.7.2 Sensitivity analyses

I also checked the influence of each individual SNP on the outcome using a leave one out approach. I created 36 additional PRSs for mothers and offspring excluding one SNP at a time. Given that there was no deviation in effect estimates when leaving out individual SNPs, I was able to use the PRS including all 36 SNPs in my analyses. Results from leave-one-out analyses are shown in Appendices 6.5-6.15. I also tested the associations between maternal PRS and potential confounders as a *post hoc* check for potential pleiotropic effects.

6.2.7.3 Replication analysis of previous ALSPAC studies

In addition, I used PRS including four offspring *ADH* genetic variants (*ADH1A* rs975833 and rs2866151, *ADH1B* rs4147536 and *ADH7* rs284779) found to be associated with child health outcomes in previous ALSPAC studies (Lewis et al., 2012; Murray et al., 2016) to test the association with ADHD risk in offspring.

6.3 RESULTS

An overview of study sample characteristics used in the analyses and stratified by maternal drinking status during pregnancy is shown in Table 6.4. In all the cohorts, mothers who reported drinking were older and better educated, compared to non-drinking mothers.

Table 6.4. Overview of study sample characteristics

	ALSPAC		GenR		MoBa	
	Maternal alcohol consumption during pregnancy					
	No N=1,125	Yes N=2,573	No N=1,004	Yes N=1,659	No N=6,536	Yes N=1,357
Confounders						
Mother's age in years (mean and SD)	28 (4.5)	30 (4.3)	30 (4.8)	32 (4.1)	30 (4.3)	32 (3.9)
Mother's education						
Primary	14%	8%	10%	2%	1%	1%
Secondary	71%	69%	49%	28%	27%	19%
Higher	15%	23%	41%	70%	72%	80%
Financial difficulties*						
No	42%	40%	80%	90%	87%	86%
Yes	58%	60%	20%	10%	13%	14%
Marital status						
Married	84%	85%	92%	92%	98.5%	98%
Single/not married	16%	15%	8%	8%	1.5%	2%
Depression symptoms**	9%	10%	8%	5%	5%	6%
Anxiety symptoms	12%	14%	10%	6%		
Mothers ADHD symptoms					2%	3%
Parity						
1st	53%	45%	57%	61%	51%	40%
2nd	33%	37%	30%	30%	33%	39%
3rd+	14%	18%	13%	9%	16%	21%
Mother smoked during pregnancy	15%	17%	17%	25%	5%	7%
Offspring ADHD symptoms above the 85th percentile threshold	13%	14%	13%	15%	12%	12%

*Note: *In ALSPAC, financial difficulties were measured with 5 items questionnaire: 1) Difficulty in affording food; 2) Difficulty in affording clothing; 3) Difficulty in affording heating 4) Difficulty in affording accommodation 5) Difficulty in affording things for baby. In GenR, financial difficulties were assessed with single item question: Difficulty in paying food, rent, bills and suchlike. In MoBa, financial difficulties were assessed with single item question: Have you experienced financial problems?; **In MoBa, depression and anxiety symptoms were assessed together*

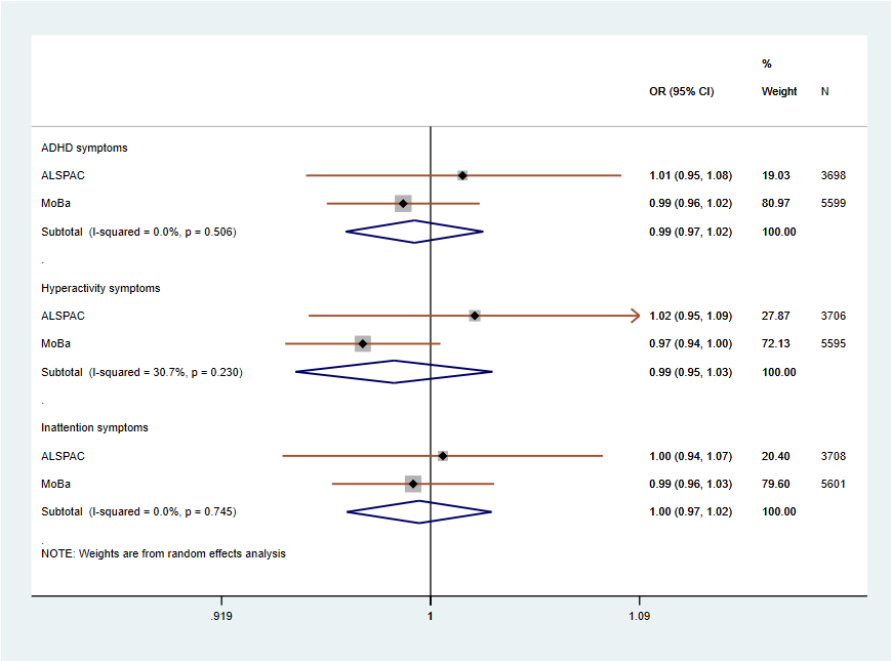
6.3.1 Maternal PRS analysis

To maximise data available across the cohorts, meta-analysis for maternal PRS was conducted using results from model 2 (maternal PRS adjusted for offspring PRS).

The pooled estimate for the association of maternal PRS with high risk of maternal reported ADHD symptoms in offspring in model 2 did not show clear evidence for an association (OR_{ADHD}=0.99, 95%CI 0.97, 1.02; OR_{HYP}=0.99, 95%CI 0.95, 1.03; OR_{INA}=1.00, 95%CI 0.97, 1.02) (Figure 6.4). However, in MoBa I found a negative association between maternal PRS and high risk of maternal reported ADHD

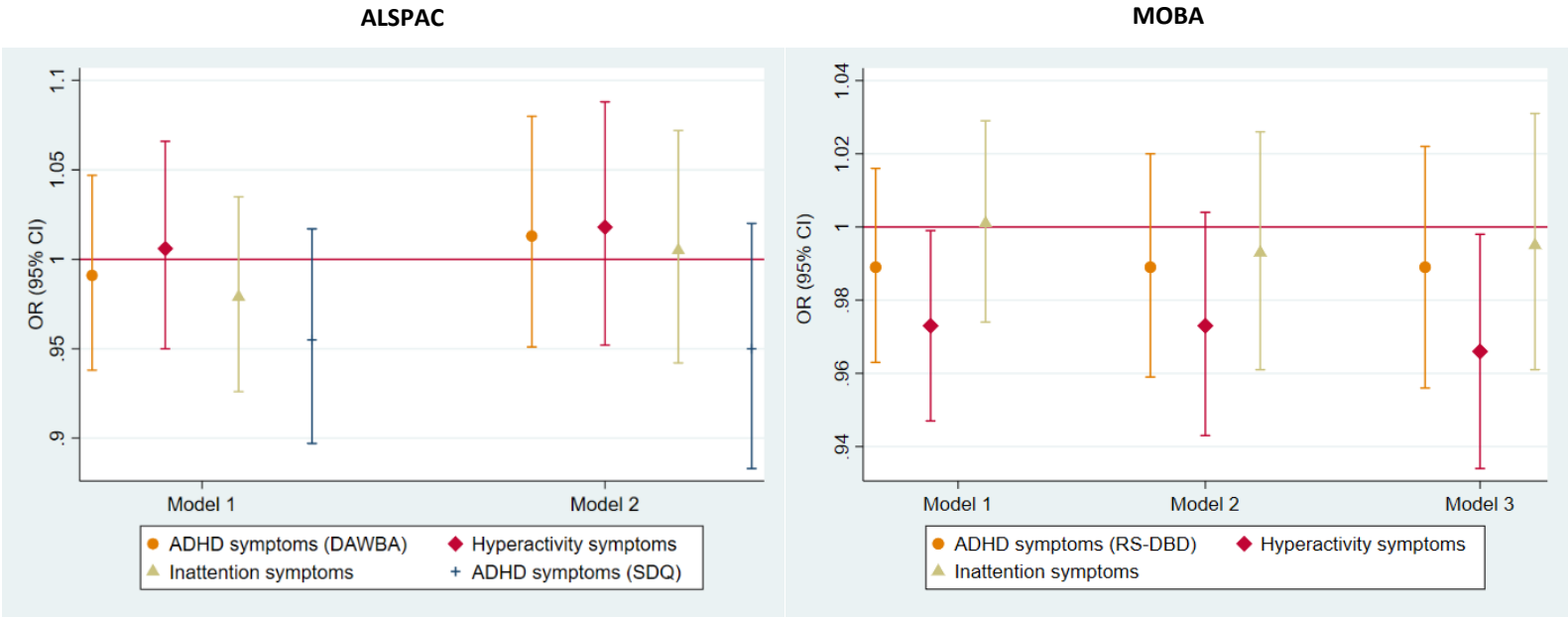
hyperactivity symptoms in offspring in model 1 (maternal PRS) and model 3 (adjusted for offspring and paternal PRS) (Figure 6.5 and Table 6.5). This finding was not replicated in ALSPAC using high risk of maternal reported ADHD symptoms (Figure 6.5 and Table 6.6). Similarly, the results did not change when I used secondary outcome measures in ALSPAC (Appendices 6.16 and 6.17).

Figure 6.4. Meta-analysis of maternal PRS on high risk of maternal reported offspring ADHD symptoms in ALSPAC and MoBa



Note: Model 2 - maternal PRS adjusted for offspring PRS and 10 ancestry principal components

Figure 6.5. Associations between maternal PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC and MoBa



Note: Model 1 – only maternal PRS; Model 2 – maternal PRS adjusted for offspring PRS; Model 3 - maternal PRS adjusted for offspring and paternal PRS; All analyses are adjusted for 10 ancestry principal components. In MoBa, also for birth year and genotyping batch; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) - secondary measure; Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Table 6.5. Associations between maternal PRS and high risk of maternal reported offspring ADHD symptoms in MoBa (primary analyses)

	Model 1			Model 2			Model 3			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (RS-DBD)	0.99	0.963, 1.016	0.418	0.99	0.959, 1.020	0.488	0.99	0.956, 1.022	0.494	5,599
Hyperactivity symptoms	0.97	0.947, 0.999	0.042	0.97	0.943, 1.004	0.082	0.97	0.934, 0.998	0.039	5,595
Inattention symptoms	1.00	0.974, 1.029	0.940	0.99	0.961, 1.026	0.659	1.00	0.961, 1.031	0.798	5,601

Note: Model 1 – only maternal PRS; Model 2 – maternal PRS adj. for offspring PRS; Model 3 – maternal PRS adj. for offspring and paternal PRS; all analyses adjusted also for 10 ancestry principal components, birth year and genotyping batch; Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Table 6.6. Associations between maternal PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC (primary analyses)

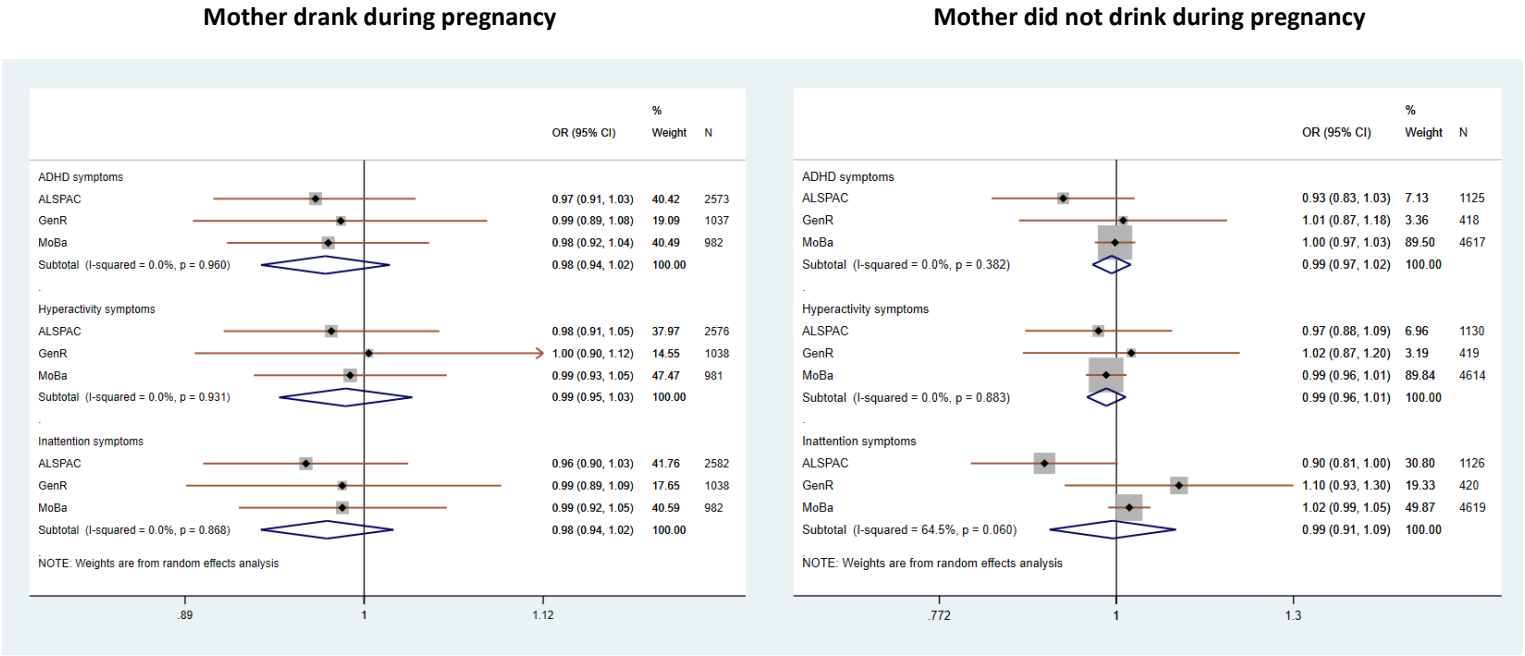
	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.99	0.938, 1.047	0.746	1.01	0.951, 1.080	0.682	3,698
Hyperactivity symptoms	1.01	0.950, 1.066	0.827	1.02	0.952, 1.088	0.608	3,706
Inattention symptoms	0.98	0.926, 1.035	0.452	1.01	0.942, 1.072	0.872	3,708
ADHD symptoms (SDQ)	0.96	0.897, 1.017	0.148	0.95	0.883, 1.020	0.159	3,736

Note: Model 1 – only maternal PRS; Model 2 – maternal PRS adj. for offspring PRS; all analyses adjusted also for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) - secondary measure

6.3.2 Offspring PRS analysis

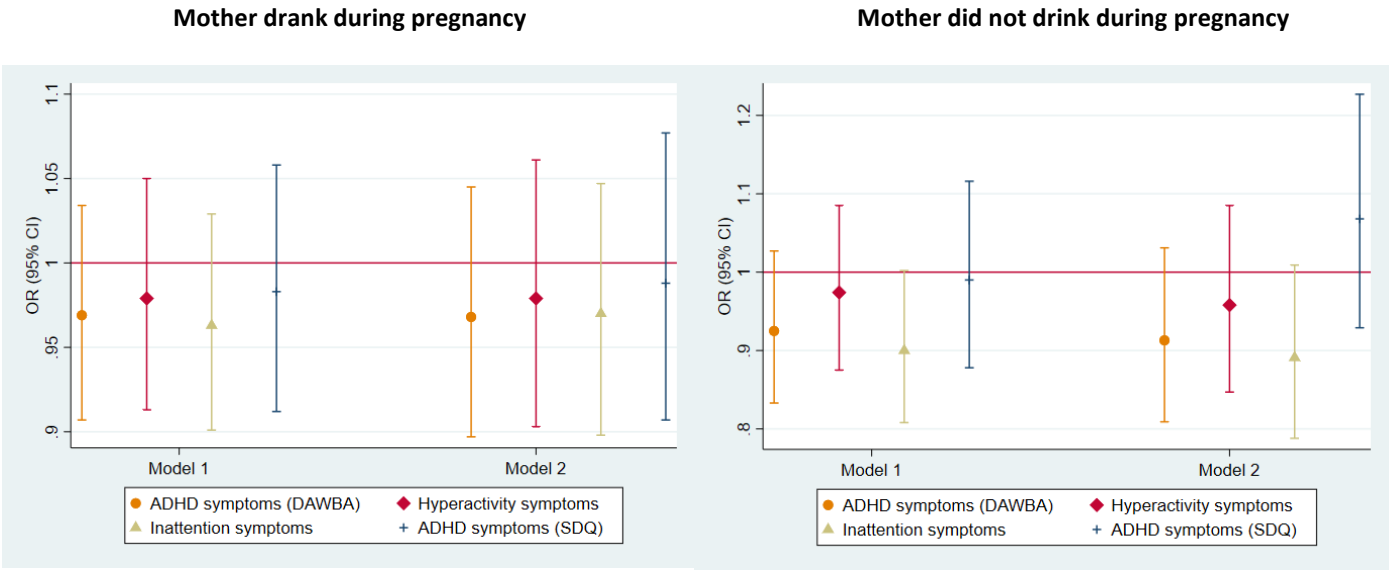
The pooled estimate of the association between offspring PRS and high risk of maternal reported ADHD symptoms in offspring using model 1 (offspring PRS) found no strong evidence of an association. This remained consistent regardless of drinking status during pregnancy (Drinking: OR_{ADHD}=0.98, 95%CI 0.94, 1.02; OR_{HYP}=0.99, 95%CI 0.95, 1.03; OR_{INA}=0.98, 95%CI 0.94, 1.02; No drinking: OR_{ADHD}=0.99, 95%CI 0.97, 1.02; OR_{HYP}=0.99, 95%CI 0.96, 1.01; OR_{INA}=0.99, 95%CI 0.91, 1.09) (Figure 6.6). These results did not change after adjusting for maternal PRS (model 2) or maternal and paternal PRS (model 3) in ALSPAC and MoBa (Figure 6.7 and 6.8, Tables 6.7-6.10). Similarly, when I used secondary outcome measures in GenR and ALSPAC, I found no strong evidence of an association between offspring PRS and ADHD risk in offspring (Figure 6.9 and Table 6.11; Appendices 6.18-6.20).

Figure 6.6. Meta-analysis of offspring PRS on high risk of maternal reported offspring ADHD symptoms across the cohorts



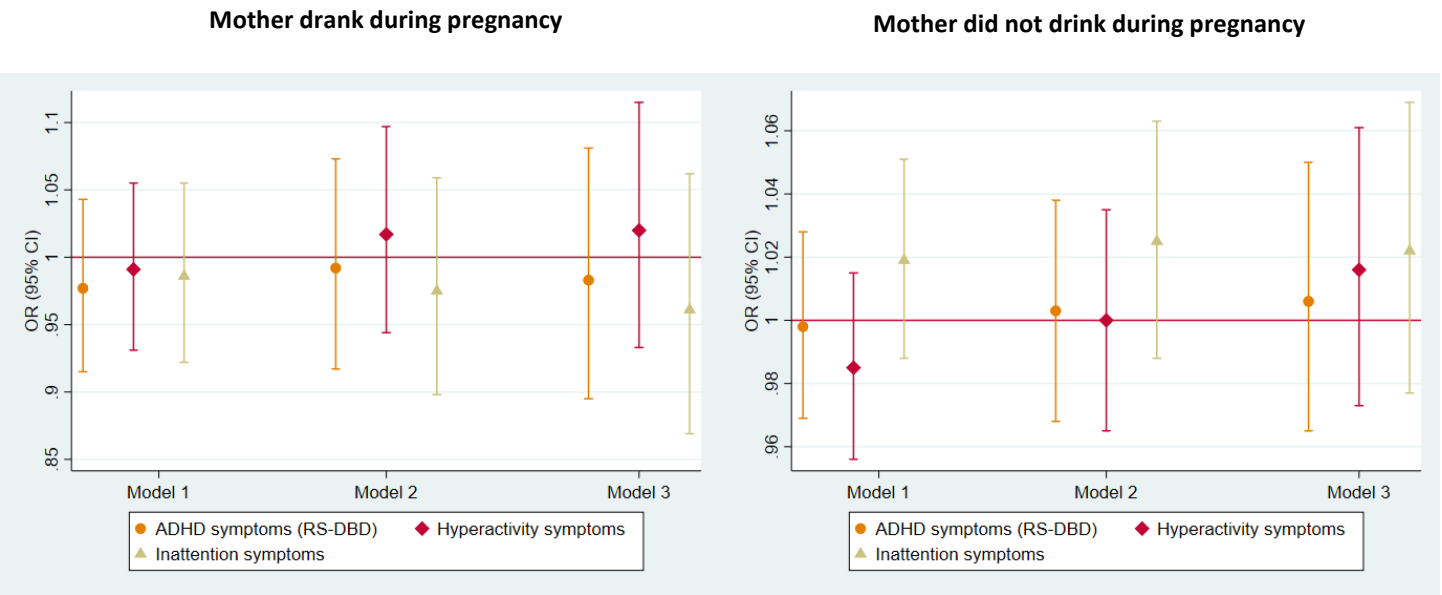
Note: Model 1 – only offspring PRS and adjusted for 10 ancestry principal components

Figure 6.7. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC stratified by maternal drinking status in ALSPAC (primary analyses)



Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adjusted for maternal PRS; all analyses are adjusted for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Figure 6.8. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in MoBa stratified by maternal drinking status in MoBa (primary analyses)



Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adjusted for maternal PRS; Model 3 – offspring PRS adjusted for maternal and paternal PRS; all analyses are adjusted for 10 ancestry principal components, birth year and genotyping batch; Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Table 6.7. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC if mother drank during pregnancy (primary analyses)

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.97	0.907, 1.034	0.341	0.97	0.897, 1.045	0.400	2,573
Hyperactivity symptoms	0.98	0.913, 1.050	0.552	0.98	0.903, 1.061	0.599	2,576
Inattention symptoms	0.96	0.901, 1.029	0.266	0.97	0.898, 1.047	0.431	2,582
ADHD symptoms (SDQ)	0.98	0.912, 1.058	0.643	0.99	0.907, 1.077	0.787	2,606

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; all analyses adjusted also for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Table 6.8. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC if mother did not drink during pregnancy (primary analyses)

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.93	0.833, 1.027	0.145	0.91	0.809, 1.031	0.142	1,125
Hyperactivity symptoms	0.97	0.875, 1.085	0.635	0.96	0.847, 1.085	0.502	1,130
Inattention symptoms	0.90	0.808, 1.002	0.055	0.89	0.788, 1.009	0.069	1,126
ADHD symptoms (SDQ)	0.99	0.878, 1.116	0.868	1.07	0.929, 1.227	0.356	1,130

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; all analyses adjusted also for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Table 6.9. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in MoBa if mother drank during pregnancy (primary analyses)

	Model 1			Model 2			Model 3			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (RS-DBD)	0.98	0.915, 1.043	0.485	0.99	0.917, 1.073	0.842	0.98	0.895, 1.081	0.728	982
Hyperactivity symptoms	0.99	0.931, 1.055	0.778	1.02	0.944, 1.097	0.656	1.02	0.933, 1.115	0.666	981
Inattention symptoms	0.99	0.922, 1.055	0.692	0.98	0.898, 1.059	0.548	0.96	0.869, 1.062	0.431	982

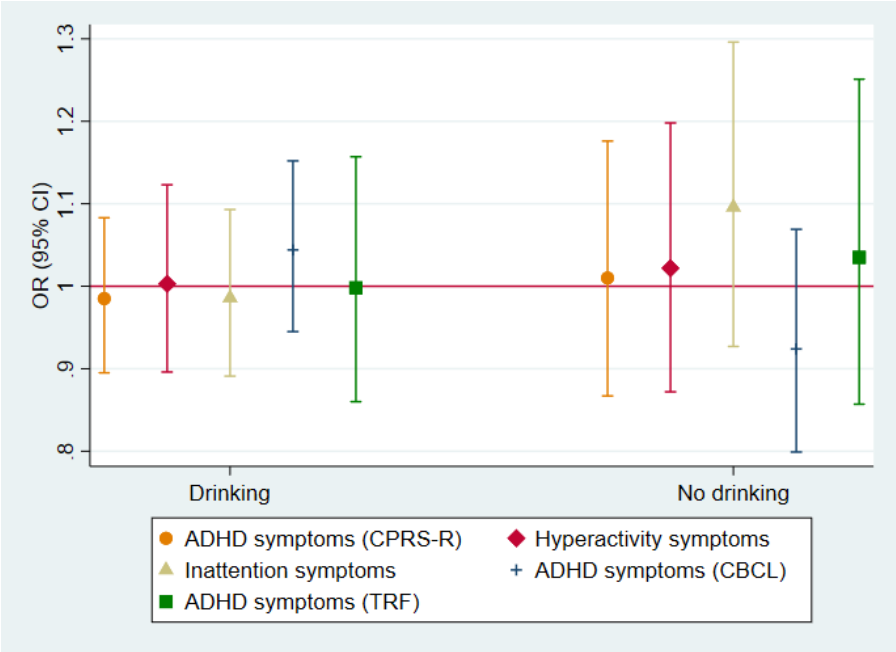
Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; Model 3 – offspring PRS adj. for maternal and paternal PRS; all analyses adjusted for 10 ancestry principal components, birth year and genotyping batch; Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Table 6.10. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in MoBa if mother did not drink during pregnancy (primary analyses)

	Model 1			Model 2			Model 3			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (RS-DBD)	1.00	0.969, 1.028	0.904	1.00	0.968, 1.038	0.881	1.01	0.965, 1.050	0.766	4,617
Hyperactivity symptoms	0.99	0.956, 1.015	0.318	1.00	0.965, 1.035	0.986	1.02	0.973, 1.061	0.479	4,614
Inattention symptoms	1.02	0.988, 1.051	0.242	1.03	0.988, 1.063	0.193	1.02	0.977, 1.069	0.353	4,619

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; Model 3 – offspring PRS adj. for maternal and paternal PRS; all analyses adjusted also for 10 ancestry principal components, birth year and genotyping batch; Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Figure 6.9. Associations between offspring PRS and high risk of maternal and teacher reported offspring ADHD symptoms in GenR stratified by maternal drinking status (primary and secondary analyses)



Note: Model 1 – only offspring PRS adjusted for 10 ancestry principal components; Revised Conner's Parent Rating Scale (CPRS-R); Child Behavior Checklist (CBCL) – secondary measure; Teacher Report Form (TRF) -secondary measure

Table 6.11. Associations between offspring PRS and high risk of maternal and teacher reported offspring ADHD symptoms in GenR (primary and secondary analyses)

	Mother drank during pregnancy				Mother did not drink during pregnancy			
Outcome	**OR**	**95% CI**	**P-value**	**Sample size**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (CPRS-R)	0.99	0.895, 1.083	0.750	1,037	1.01	0.867, 1.176	0.903	418
Hyperactivity symptoms	1.00	0.896, 1.123	0.958	1,038	1.02	0.872, 1.198	0.790	419
Inattention symptoms	0.99	0.891, 1.093	0.794	1,038	1.10	0.927, 1.296	0.285	420
ADHD symptoms (CBCL)	1.04	0.945, 1.152	0.398	1,186	0.92	0.799, 1.069	0.288	510
ADHD symptoms (TRF)	1.00	0.860, 1.157	0.976	708	1.04	0.857, 1.251	0.719	317

Note: Model 1 – only offspring PRS adjusted also for 10 ancestry principal components; Revised Conner's Parent Rating Scale (CPRS-R); Child Behavior Checklist (CBCL); Teacher Report Form (TRF). CBCL and TRF were secondary measures

6.3.3 Sensitivity analyses

My sensitivity analyses testing the associations between maternal PRS and confounders found an association with higher likelihood of not being married in MoBa, but there was no clear evidence for associations in ALSPAC (Table 6.12-6.13).

Table 6.12. Associations between maternal PRS and confounders in ALSPAC

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	-0.02	-0.084, 0.042	0.507	7,421
Maternal education	Beta	0.001	-0.017, 0.018	0.951	6,860
Financial difficulties	Beta	-0.03	-0.078, 0.018	0.217	6,691
Marital status	OR	0.98	0.949, 1.013	0.227	7,124
Depression symptoms	OR	1.02	0.982, 1.069	0.264	6,706
Anxiety symptoms	OR	0.98	0.945, 1.022	0.384	6,669
Parity	Beta	0.01	-0.004, 0.020	0.184	7,040
Maternal smoking in pregnancy	OR	0.90	0.958,1.022	0.528	7,138

Note: adjusted for 10 ancestry principal components; OR – odds ratio; 95% CI – 95% confidence intervals.

Table 6.13. Associations between maternal PRS and confounders in MoBa

Confounder	Effect estimate	Effect size	95% CI	P-value	Sample size
Maternal age	Beta	0.04	-0.049, 0.129	0.381	13,614
Maternal education	Beta	<0.001	-0.003, 0.0003	0.839	12,917
Financial difficulties	OR	1.00	0.980, 1.012	0.650	12,575
Marital status	Beta	0.001	0.0001, 0.002	0.035	13,555
Depression/Anxiety symptoms	OR	0.99	0.969, 1.014	0.454	13,503
Parity	Beta	0.002	-0.003, 0.007	0.433	13,614
Maternal ADHD symptoms	OR	1.02	0.976,1.065	0.390	8,231
Maternal smoking in pregnancy	OR	1.00	0.973, 1.016	0.627	13,540

Note: adjusted for 10 ancestry principal components; birth year and genotyping batch; OR – odds ratio; 95% CI – 95% confidence intervals

6.3.4 Replication analysis of previous ALSPAC studies

Replication analysis using offspring PRS with 4 *ADH* SNPs were consistent with the main analysis, and provided little evidence for an association between fetal alcohol exposure and high risk of maternal or teacher

reported ADHD symptoms in offspring. These results are shown in Appendices 6.21-6.31.

6.4 DISCUSSION

I used maternal and offspring genetic variants in the *ADH* and *ALDH* genes linked to alcohol consumption and metabolism to investigate whether there is a causal effect of fetal alcohol exposure on ADHD risk in offspring. Consistent with findings in previous chapters, I did not find strong evidence for a causal effect. I observed a protective effect of maternal PRS indicative of higher alcohol exposure on high risk of maternal reported offspring ADHD hyperactive-impulsive symptoms in MoBa. However, this was not replicated in ALSPAC where mothers had more prevalent daily alcohol use (16% in ALSPAC and 0.45% in MoBa) and regardless of whether ADHD symptoms were reported by mother or teacher. I did not observe associations of offspring PRS with high risk of maternal and teacher reported childhood ADHD symptoms, in any of the cohorts, or for any of the subtypes, with or without adjustment for maternal and paternal PRS where this was available, or stratification by maternal alcohol use in pregnancy.

My results are somewhat dissimilar from previous findings in ALSPAC, which found the risk of early onset conduct problems and decreased IQ to be associated with the *ADH* variants particularly in children whose mothers drank during pregnancy (Lewis et al., 2012; Murray et al., 2016). This might suggest that there could be some cognitive effects not mediated by behavioural factors, although several studies have found opposite effect (Schoemaker et al., 2013). Alternatively, these previous findings could be false positives, as these studies used a very limited number of offspring genetic variants in *ADH* genes as a proxy for fetal alcohol exposure. In addition, these four offspring SNPs were selected based on the association with the outcome. The present study was based on larger numbers of mother-offspring dyads, and importantly used all available *ADH/ALDH* variants, not just a restricted number of them selected on their effects on the outcome. Other studies that have examined the association between

maternal PAE and behavioural problems in offspring by using quasi-experimental design to account for shared genetic and environmental factors found evidence for a potential causal effect on conduct disorder symptoms measured with CBCL at age 4-11 years, somatic complaints and emotional reactiveness at age 3 years, but not ADHD symptoms (D'Onofrio et al., 2007; Lund et al., 2019). However, a study by Lund and colleagues did not observe the association with emotional reactiveness at age 5 years. Moreover, another study using a similar design in the MoBa cohort observed an association with ADHD symptoms at age 5 years measured with CPRS-R, but not with CBCL or when ADHD diagnosis was used (Eilertsen et al., 2017). Although these studies used a sibling comparison design which enables to account for shared genetic and environmental confounds between mothers and offspring, they cannot prove causality. The association may be still affected by non-shared individual specific factors and measurement error, as well as familial confounding can also change over time (D'Onofrio et al., 2014; Frisell et al., 2012). Alternatively, the genetic variants used in this study can help to overcome the limitation of unmeasured confounding.

Triangulating findings across the studies based on different study designs which have a different source of bias can provide more support on whether a causal relationship exists. This is why, given that the results are not consistent across the studies, I am able to conclude that there are unlikely to be large effects of PAE on ADHD.

In addition, a common limitation of previous studies reporting a positive association between PAE, conduct disorder and ADHD symptoms (e.g., Murray et al. (2016), Lund et al. (2019), D'Onofrio et al. (2007) and Eilertsen et al. (2017)) is that they were based on outcomes that were measured using maternal report. In Chapter 5 I found inconsistent findings when offspring ADHD symptoms were reported by mothers compared to teachers. This is not unexpected, as several studies had previously shown informant discrepancies in the assessment of child mental health problems which may be affected by factors such as mothers' own mental health and

socioeconomic status (Collishaw et al., 2009; De Los Reyes and Kazdin, 2005). Differences between findings in previous studies and this study may be also related to the scales used for ADHD assessment, as was found by Eilertsen and colleagues and I observed in Chapter 5. The child's age at the time of assessment and severity of the ADHD symptoms may also have an impact on the observed results. It has been shown that presentation and manifestation of ADHD and other behavioural symptoms, and diagnosis change from preschool to adolescence (Bunte et al., 2014; Curchack-Lichtin et al., 2014; Martel et al., 2017). This may lead to different findings across development as ADHD symptoms have been found to decline with age (Faraone et al., 2006). It is therefore possible that observed associations in previous studies may be influenced by reporter bias, child age and scales used for ADHD assessment and methods that do not sufficiently account for unmeasured confounds.

6.4.1 Strengths and limitations

Currently there are few studies which have investigated the effects of fetal alcohol exposure on child mental health outcomes by using genetic variants associated with alcohol consumption and metabolism as a proxy for fetal alcohol exposure. Compared with previous studies in ALSPAC this study uses a more comprehensive approach for identifying genetic variants affecting alcohol metabolism. I also compared findings across three international longitudinal cohorts, of which one cohort includes genetic data from both parents and offspring. Having trio genetic data enables to properly account for shared genetics and overcome potential biases such as dynastic effects and assortative mating (Davies et al., 2019).

Dynastic effects (also known as genetic nurturing effects) are effects observed between parent's genotype on offspring outcomes which are mediated via parent's phenotype (Davies et al., 2019). For example, a study using PRS for educational attainment based on parental non-transmitted alleles (which are free from genetic transmission between parents and offspring) found an effect on offspring educational attainment indicating

that dynastic effects can have an impact on offspring educational attainment via parental environmental effects (Kong et al., 2018).

Similarly, assortative mating can have an effect on offspring outcomes as partner selection may be based on specific phenotypes, and partners may influence each other's phenotypes (such as alcohol behaviour) (Hartwig et al., 2018). It has been shown that similarities in partners alcohol consumption are also genetically influenced (Howe et al., 2019) and therefore it is important to adjust for both maternal and paternal genotype when estimating the effect on offspring outcomes.

However, several limitations should also be considered. First, sample size may have been too small to detect a true effect of fetal alcohol exposure on offspring ADHD risk. Although MR studies normally require sample sizes with tens of thousands of individuals, this can be difficult to gain in the context of intergenerational research and in pregnancy substance use exposures, as many women reduce/stop using substances when planning pregnancy and while being pregnant. Second, although MR and PRS analyses are less affected by confounding, as discussed in Chapter 5 (see section 5.1 "Introduction") assumptions 2 and 3 cannot be fully verified, and the risk of horizontal pleiotropy where the genetic variant directly affects the outcome still remains, even if an effect is observed. Furthermore, considering that it is not possible to directly measure the level of alcohol that the fetus is exposed to, I could not test assumption 1 either. Third, it is not possible to measure fetal blood alcohol levels to examine whether a dose-response relationship exists. Fourth, maternal alcohol consumption during pregnancy was based on self-reports and mothers may have underreported their prenatal alcohol use due to social desirability bias. This may have caused bias in the offspring PRS analyses where I stratified analyses based on maternal drinking status during pregnancy. Fifth, it is possible that lack of effects could be also influenced by included dichotomized outcome measures as this results in loss of statistical power. Very often, the scales used in ADHD assessment (SDQ, CBCL, CPRS-R) generate skewed distributions and are not always the best

measures to use in general population studies (Swanson et al., 2012). Alternatively, continuous measures associated with ADHD symptoms could be more sensitive measures to use for investigating effects of fetal alcohol exposure. Research suggests that ADHD symptoms across a population are continuously distributed, and ADHD diagnosis is the extreme end of a trait (Ahmad and Hinshaw, 2017; Larsson et al., 2012). Furthermore, it has been suggested that one approach to investigate causal pathways is to include intermediate endophenotypes (such as reaction time, response inhibition and working memory) associated with ADHD (Andreou and Kuntsi, 2005; Kuntsi et al., 2014; Kuntsi et al., 2010). One such study found that reaction time and reaction time variability captured 85% and impaired response inhibition 13% of the familial variance of ADHD, suggesting that reaction time could be a promising cognitive target for genetic investigations (Kuntsi et al., 2010). Additionally, other studies have shown that reaction time and omission errors tasks were separately associated with ADHD hyperactive-impulsive and inattention symptom domains (Kuntsi et al., 2014). Furthermore, another study found that cognitive and brain function measures can separate individuals with more persistent ADHD from childhood to young adulthood (Michelini et al., 2017).

Sixth, longitudinal birth cohorts may be affected by selection bias if some groups are under-represented in the initial recruitment. Selective attrition over time can also affect representativeness, which may cause biased exposure-outcome associations (Munafò et al., 2018). For example, in MoBa women who smoked during pregnancy, lived alone and had two previous births were under-represented (Nilsen et al., 2009) and in GenR women who continued to participate in the study were older and better educated (Kooijman et al., 2016). In addition, analyses restricted to live births can be affected by some degree of selection bias, in the form of collider bias (Liew et al., 2015), although it has been found that live birth bias is unlikely to affect studies investigating perinatal factors (Heinke et al., 2020).

6.5 CHAPTER SUMMARY

In this chapter I investigated whether there is a causal effect of fetal alcohol exposure on ADHD risk in offspring by using maternal and offspring genetic variants from alcohol metabolising genes. My results did not find strong support for a causal effect of fetal alcohol exposure on ADHD risk in offspring.

Chapter 7 DISCUSSION

In this thesis I investigated whether there is a causal effect of maternal smoking, alcohol, and caffeine use during pregnancy on ADHD risk in offspring. I used different research methods to triangulate evidence and evaluate support for a causal effect. These methods were a systematic review (Chapter 2), a Phenome-Wide Association Study (PheWAS) (Chapter 4), a negative control (Chapter 5) and polygenic risk scores (PRS) analyses (Chapter 5 and 6). As well as using data from ALSPAC, I also replicated analyses in GenR and MoBa and meta-analysed the results across the cohorts. In this chapter I discuss the main findings from each chapter, before combining the overall evidence from my research in the light of its strengths and limitations. I will also provide suggestions for future research.

7.1 SUMMARY OF FINDINGS

7.1.1 Prenatal smoking, alcohol and caffeine exposure and offspring externalising disorders: A systematic review

In Chapter 2, I conducted a systematic review where I aimed to examine whether there is evidence for a causal relationship between maternal smoking, alcohol and caffeine use during pregnancy, and attention-deficit hyperactivity disorder (ADHD), conduct disorder (CD) and oppositional-defiant disorder (ODD) in offspring by synthesising existing research. Given the high comorbidity between ADHD, CD and ODD, I investigated whether the associations would differ between these disorders and each exposure, as this could provide important aetiological clues.

I found evidence for an association between maternal smoking during pregnancy and ADHD in offspring. Based on the characteristics and results of included studies, I concluded that the association is unlikely to be causal. The majority of studies were on the relationship between smoking and ADHD, and studies on alcohol and caffeine exposure and CD and ODD offspring outcomes were even less conclusive.

I also identified several limitations and gaps in the current research. For example, studies varied greatly on the number of confounders adjusted for in analyses, which may lead to bias because of residual confounding. Of note, none of the studies accounted for partner substance use during pregnancy and only a few studies adjusted for maternal mental health during pregnancy. In addition, studies differed in terms of assessment of exposures and the age of ADHD assessment in offspring. Although several studies have shown that childhood ADHD persists into adulthood, other studies have also found that ADHD symptoms change across development. Therefore, lack of evidence may be influenced by changes at different developmental stages.

Many of the included studies were based on binary exposures and assessed retrospectively, which may lead to recall bias. The majority of the studies on ADHD were based on overall ADHD diagnosis and only a few studies investigated ADHD hyperactive-impulsive and inattention symptom domains separately, so the evidence was weaker for the individual symptoms' components. Despite the scant evidence base, some studies found that maternal prenatal substance use can have a distinct effect on ADHD symptom domains.

7.1.2 Maternal and child genetic liability for smoking and caffeine consumption and child mental health: A Phenome-Wide Association Study in the ALSPAC cohort.

In Chapter 4, I used intergenerational PRS analyses to investigate the effects of maternal and child genetic liability for smoking and caffeine consumption on various child mental health outcomes, in a targeted PheWAS approach. This study had three main aims: 1) validate that the PRS for smoking (smoking initiation and lifetime smoking) and caffeine consumption are associated with consumption of these substances in pregnancy and offspring in adolescence; 2) investigate intergenerational effects by testing associations between maternal and offspring PRS and offspring outcomes in childhood before children are likely to consume these substances themselves (under age 10 years); and 3) disentangle

potential causal effects from pleiotropic effects by testing associations between maternal PRS and their own mental health outcomes during and outside of pregnancy, as well as between offspring PRS on their own mental health outcomes in adolescence.

Results from this study showed that smoking and caffeine PRS could be used as proxies for measuring smoking and caffeine consumption during pregnancy, but not during adolescence on caffeine consumption. I also found evidence for likely pleiotropic effects between maternal smoking PRS and socio-economic traits, as well as with externalising disorder symptoms in offspring. Evidence was weaker for intergenerational effects between maternal caffeine PRS and offspring outcomes in childhood. However, in this study I did not investigate ADHD symptom domains separately and given the limitations of the PheWAS design, which is meant to generate rather than test hypotheses, no strong conclusions regarding causality can be drawn.

7.1.3 Prenatal smoking, alcohol and caffeine exposure and ADHD risk in childhood: parental comparisons and polygenic risk score (PRS) analyses

In Chapter 5, I combined a negative control design and an PRS approach to investigate whether there is a causal effect of maternal smoking, alcohol, and caffeine use during pregnancy on high risk of offspring total ADHD, as well as separately for hyperactive-impulsive and inattention symptoms. Considering that negative control analyses may still be biased because of unmeasured and residual confounding, I also used genetic variants as proxies for maternal prenatal substance use to gain stronger support for causal inference. As well as using data from ALSPAC, I also conducted the same analyses in GenR and MoBa cohorts and then meta-analysed results across the cohorts, to increase statistical power.

In this study, I did not find strong support for a causal effect between maternal smoking, alcohol, or caffeine consumption during pregnancy and any of the ADHD symptom domains in offspring. Similarly to the findings

reported in Chapter 4, results with smoking PRS showed pleiotropic effects with socio-economic and mental health traits. However, I observed somewhat different findings between maternal and teacher reported ADHD symptoms, as well as between the different scales used for ADHD assessment. Therefore, future research should further investigate whether different scales are measuring the same construct of ADHD.

7.1.4 Maternal and offspring polygenic risk score (PRS) analyses of fetal alcohol exposure and ADHD risk in offspring

In Chapter 6, I used maternal and offspring genetic variants from alcohol metabolising genes (*ADH* and *ALDH*) as proxies for fetal alcohol exposure to investigate their association with high risk of offspring total ADHD, as well as hyperactive-impulsive and inattention symptoms. As in Chapter 5, I used data from three longitudinal birth cohorts: ALSPAC, GenR and MoBa.

I tested the association between maternal PRS and ADHD outcomes using three models: 1) only maternal PRS; 2) maternal PRS adjusted for offspring PRS; and 3) maternal PRS adjusted for offspring and paternal PRS. I ran maternal analyses in the full sample as stratifying on maternal prenatal drinking status may induce a collider bias.

I used three models also in offspring PRS analyses: 1) only offspring PRS; 2) offspring PRS adjusted for maternal PRS; and 3) offspring PRS adjusted for maternal and paternal PRS. These analyses were stratified based on maternal drinking status during pregnancy as compared to maternal PRS analyses there was no risk for a collider bias in offspring PRS analyses. However, given differences in availability of genetic data across the cohorts, I was able to conduct analyses in all three models only in MoBa.

Similarly to the findings reported in Chapter 5, I did not find strong support for a causal effect of fetal alcohol exposure on offspring ADHD risk. However, lack of evidence for effects may be influenced by low statistical power due to the small sample size and dichotomised outcome measures. Considering the complex nature of the ADHD phenotype, more sensitive

measures for ADHD might be necessary to detect potential causal effects. In general, my findings are in line with other studies which have concluded that low level of alcohol consumption during pregnancy do not have a substantial effect on offspring mental health outcomes.

7.2 OVERALL FINDINGS

This thesis aimed to investigate whether there is a causal effect of maternal smoking, alcohol and caffeine consumption during pregnancy on offspring ADHD risk. The observed associations could be explained by several scenarios:

1. There is a true causal effect of maternal prenatal substance use on ADHD risk in offspring.
2. There is no causal effect and the association between maternal prenatal substance use and ADHD risk in offspring is explained by confounding.
3. The effect is observed by chance.
4. The effect is observed as a result of the bias in applied method.
5. The effect could be causal, but the current effect estimates are biased by environmental and genetic confounding.

In this thesis I did not find strong support for a causal effect of maternal prenatal smoking, alcohol or caffeine use on offspring ADHD risk (Chapter 4, 5 and 6). The associations observed in the negative control analyses were inconsistent across the cohorts, and sensitivity analyses did not find evidence for a causal effect of alcohol and caffeine exposure. However, some suggestive evidence was found in support of a causal effect between prenatal smoking exposure and only offspring maternal-reported ADHD symptoms in GenR and MoBa, (Chapter 5). Still, the evidence was weak and inconsistent across different scales and reporters used in ADHD assessment. Therefore, these observed associations are likely to be affected by genetic confounding.

Furthermore, findings using genetic analyses which are less affected by confounding such as a PheWAS approach (Chapter 4) indicated that the

observed associations between maternal smoking PRS and offspring externalising disorder symptoms, as well as with ADHD symptoms are likely explained by shared genetics between mother and offspring. Similarly, maternal smoking PRS analyses in Chapter 5 observed pleiotropic effects with multiple socio-economic traits. Additionally, findings from the systematic review (Chapter 2) where I included various study designs of which some accounted for environmental and genetic confounders suggested that the association between maternal smoking during pregnancy and ADHD in offspring is confounded. Therefore, taken together results from multiple methods, my findings do not support a causal effect of maternal prenatal smoking on offspring ADHD risk.

Moreover, it is also possible that some associations of prenatal alcohol exposure observed in MoBa were because of chance, as these were not replicated in other cohorts (Chapter 6). In addition, as stated above, associations of smoking exposure found in the negative control analyses in GenR and MoBa could be a result of unmeasured confounding (Chapter 5), as PheWAS and PRS analyses did not confirm potential causal effects (Chapter 4 and 5).

Nevertheless, considering the limitations in my studies and methods, I cannot completely rule out the possibility that there still may be a causal maternal environmental (pre- and postnatal) effect, as well as the association could be explained by genetic transmission from mother to offspring.

A summary of causal inference approaches, including biases, limitations and main findings is listed in Table 7.1.

Table 7.1 Summary of causal inference approaches

Causal inference approach	Bias addressed	Limitations of approach	Main findings
PheWAS (Chapter 4)	Measured and unmeasured confounding	Low power and horizontal pleiotropy	- Positive association between maternal smoking PRS and externalising disorder symptoms in offspring in childhood - Positive association between offspring smoking PRS and externalising disorder symptoms in childhood - The magnitude of effect estimates of maternal and offspring smoking PRS on externalising disorder symptoms in childhood was similar - Positive association between maternal smoking PRS and sensation type of personality traits outside of pregnancy - Positive association between offspring smoking PRS and externalising disorder symptoms, as well as extroverted personality traits in adolescence - No strong evidence for intergenerational effects of maternal caffeine PRS on offspring externalising disorder symptoms in offspring
Negative control analyses (Chapter 5)	Measured confounding shared between mothers and fathers	Unmeasured and residual confounding, self-reported exposure	- Suggestive causal effect of maternal prenatal smoking on high risk of offspring maternal reported ADHD symptoms in GenR and MoBa - No strong support for a causal effect between maternal prenatal alcohol and caffeine consumption and ADHD risk in offspring in any of the cohorts
PRS analyses (Chapter 5 and 6)	Measured and unmeasured confounding and maternal self-reported exposure	Low power and horizontal pleiotropy	- Pleiotropic associations observed with maternal lifetime smoking PRS and socio-economic and mental health traits in ALSPAC and MoBa - No associations observed between maternal alcohol and caffeine PRS and high risk of ADHD symptoms in offspring - No support for a causal effect between fetal alcohol exposure (PRS for alcohol metabolising genetic variants) and high risk of ADHD symptoms in offspring

7.3 STRENGTHS AND IMPLICATIONS

7.3.1 Triangulation

The major strength of this thesis is the triangulation of evidence through the use of different research methods, each with different strengths, weaknesses and sources of potential bias. Applying various approaches for the same research question enables me to draw stronger conclusions on causal effects. Given that each method has different source of biases, it is unlikely that all these methods are biased in the same way. Therefore, methods used in this thesis enable me to account for both environmental and genetic confounding that can affect the association between maternal prenatal substance use and ADHD risk in offspring. Furthermore, I used both negative control and PRS analyses to investigate causal effects of maternal prenatal substance use on ADHD symptom domains. In addition to ALSPAC, I used data from GenR and MoBa cohorts to increase statistical power and replicate findings which can also provide more credibility to observed results.

As mentioned above, the main principle of using triangulation is to apply multiple approaches which address the same causal question but rely on different assumptions and will be subject to different sources and direction of bias. If consistent results are observed using these methods and across the different study populations then stronger conclusions on causal effects can be made, as it would be unlikely that the results are explained by the different biases affecting each type of study (often in opposite directions or unequal in size). It has previously been noted that when investigating prenatal effects, researchers should consider multiple approaches (Lawlor et al., 2017). For example, it is recommended that Mendelian Randomization (MR) studies should be integrated with other methods, as very often MR studies on pregnancy exposures may be underpowered and assumptions could be violated (Lawlor et al., 2017). Therefore, negative control studies (such as parental and sibling comparison or cross-cohort comparison) provide an opportunity to address the same research question in a larger sample.

As described in section 7.2 (“Overall findings”) my findings across cohorts and different methods did not find evidence for a causal effect of maternal prenatal substance use and ADHD risk in offspring. Use of both observational (Chapter 5) and genetic analyses (Chapter 4, 5 and 6) show how we can triangulate evidence to example causal relationship.

7.3.2 Multiple measures of ADHD

Currently there are few studies that have investigated ADHD symptom domains separately, and many studies in the published research have mostly relied on maternal report. My findings in Chapter 5 showed that results varied depending on whether ADHD symptoms were reported by mothers or teachers and which questionnaire was used for the ADHD assessment. This further highlights the need to focus more on the phenotyping of ADHD, as this could be also one of the reasons why I did not find strong evidence for an effect. Alternatively, more refined phenotyping may show that there is no effect of maternal prenatal substance use on offspring ADHD risk.

7.3.3 Public health and clinical implications

Considering the high economic and societal burden of ADHD, it is crucial to improve current knowledge about the risk factors that may have a causal effect on ADHD risk. The Developmental origins of Health and Disease (DoHaD) hypothesis suggests that maternal health behaviours during pregnancy can have a causal effect on child health outcomes (Swanson and Wadhwa, 2008). Therefore, if maternal smoking, alcohol, and caffeine consumption during pregnancy have a causal effect on ADHD risk in offspring, these harmful behaviours could be potential targets for public health interventions, or this evidence could be used to further strengthen existing interventions. Evidence do not suggest a causal effect of prenatal smoking and caffeine use on offspring ADHD, but there may be potential causal effects of alcohol and public health interventions could focus on this risk factor in relation to offspring ADHD. Furthermore, considering that there is a genetic overlap between substance use and ADHD, mothers who

smoke during pregnancy may pass on genes to their children that increase the risk for ADHD. This knowledge can help to detect children at risk for ADHD. For example, children at risk for ADHD could benefit from interventions that can help them to cope better with their symptoms and therefore also reduce later negative outcomes.

7.4 LIMITATIONS

In each chapter I have discussed potential limitations that may have influenced my results. Here I describe the main challenges that were common across multiple chapters.

7.4.1 Attrition in cohort studies

A common limitation of longitudinal birth cohorts is attrition over time. Missing data due to loss to follow up or irregular response rate may lead to selection bias and also affect effect estimates in exposure-outcome associations (Biele et al., 2019; Mostafa and Wiggins, 2015). Furthermore, loss to follow up can also weaken the representativeness of the study population as people with certain socio-demographic characteristics are more likely to drop out (Mostafa and Wiggins, 2015). Considering that in my analyses attrition was around 50% in all the cohorts by the time children were aged around 7-8 years, it is possible that observed results may be affected by selection bias. This may lead to either over or under estimation of the association between exposure and outcome (Hernan et al., 2004).

Multiple imputation has been used to increase sample size and account for missing data, but findings have not differed substantially between imputed and non-imputed datasets in previous studies (Easey et al., 2020; Gustavson et al., 2017). Although I did not perform multiple imputation, I restricted negative control analyses to complete data (Chapter 5) and results remained similar. Inverse participation-probability weighting (IPPW) has also been suggested as one potential method to reduce selection bias due to participation factors, such as education which may predict participation in the study (Biele et al., 2019). However, it is also noted that IPPW is not a sufficient method to reduce selection bias if the exposure-

outcome association is affected by unmeasured confounders, as may be the case between maternal prenatal smoking and offspring ADHD (Biele et al., 2019).

7.4.2 Selection bias

My findings could have also been affected by selection bias related to selection on becoming pregnant and live births. For example, women who agreed to participate in the study had a "successful" pregnancy, but there is evidence that maternal substance use before pregnancy may increase the risk for spontaneous abortion and difficulties to conceive (Lassi et al., 2014; Sharma et al., 2013), as well as substance use during pregnancy may affect women's ability to carry pregnancy to term. A recent systematic review and meta-analysis on prenatal alcohol use and miscarriage found a dose-dependent association between alcohol consumption during pregnancy and increased risk of miscarriage (Sundermann et al., 2019).

Similarly, studies on prenatal smoking and caffeine exposure have found evidence of increased risk for spontaneous abortion, miscarriage and stillbirth (Greenwood et al., 2014; Pineles et al., 2014). Therefore, it is possible that women with greater prenatal substance use were not eligible to participate in the cohorts because of early fetal loss and this could also affect observed findings in my studies. As described in Chapter 6 conditioning on live birth may induce collider bias and open another pathway via unmeasured common cause between exposure, live birth and outcome, but it has been shown that live birth bias is unlikely to cause bias in studies investigating perinatal factors (Heinke et al., 2020; Liew et al., 2015; Neophytou et al., 2020).

7.4.3 Assessment of exposures

7.4.3.1 Self-reported exposures

In all the included cohorts, maternal substance use during pregnancy was measured with maternal self-reported questionnaires. Given the stigmatisation of prenatal substance use, mothers may have underreported their prenatal substance use. Although it has been shown that for more

sensitive questions the bias is stronger for in-person data collection than for self-reported questionnaires (Bowling, 2005), mothers may still have responded in the way which is seen as more favourable and underreporting is still plausible. However, using genetic variants as proxies for maternal prenatal exposures can help to overcome the limitation of social desirability bias.

Alternatively, biomarkers associated with smoking and alcohol consumption could be used as potential measures for prenatal smoking and alcohol use. For example, ethyl glucuronide (EtG) is a biomarker of fetal ethanol exposure that can be measured in newborns and could be used to detect alcohol consumption in late pregnancy (Eichler et al., 2016). This measure has been found to be more precise than retrospectively self-reported prenatal alcohol consumption (Eichler et al., 2016).

For prenatal smoking exposure, measuring cotinine (the primary metabolite of nicotine, and therefore a useful biomarker) has been suggested. Cotinine could be measured in urine or blood, as well as in newborns at birth. However, cotinine could be used as a marker for recent smoking, and it may still be affected by maternal metabolic variability and may not be precise enough (Dukic et al., 2007).

Although a biochemical verification of prenatal substance use may provide more accurate information, these measures could be too costly for longitudinal cohort studies, and will still be as affected by confounding as the behavioural self-reported measures.

7.4.3.2 Time-variation in exposures

My negative control analyses were performed using exposure data from the first pregnancy trimester, where both maternal and paternal exposure data were available. However it is possible that the effect of exposures on outcomes can differ between the trimesters and the effect may also depend on whether the exposure was present throughout pregnancy or not (Neophytou et al., 2020). However, one previous study on alcohol exposure found that maternal prenatal alcohol consumption had a stronger effect on

offspring conduct disorder in the first pregnancy trimester than in the third pregnancy trimester indicating that prenatal substance use may have more harmful effects on offspring health outcomes in the first pregnancy trimester (Larkby et al., 2011). However, considering that many women reduce or stop their substance use once they become aware of their pregnancy, then the effects of later substance use may be harder to detect.

Similarly, my PRS analyses were based on the assumption that genetic effects on exposure remains constant throughout pregnancy. A potential bias because of time-varying exposures has been pointed out in MR studies where the goal is to estimate a lifetime effect (Labrecque and Swanson, 2019). Therefore, it is also possible that my results may be subject to bias if duration and intensity of maternal prenatal smoking, alcohol and caffeine consumption, as well as the genetic effects on these exposures change over the course of the pregnancy.

7.4.4 Assessment of ADHD

Although all the included scales for ADHD assessment had good psychometric properties, different scales were used in all the cohorts, which may have caused measurement error when combining them together. Furthermore, ADHD symptom scores in the analyses were dichotomised due to the skewed distribution. This may have had an impact on power to detect an effect in PRS analyses (Fedorov et al., 2009). In addition, studies on prenatal alcohol exposure have indicated shared characteristics and symptom overlap between ADHD and FASD which may lead to misclassification of ADHD (Mattson and Riley, 2011). Therefore, more clear phenotyping of ADHD is needed for future studies which could help to distinguish ADHD from FASD.

Furthermore, some studies have shown that prenatal substance use may have a somewhat different effect on ADHD symptom domains, as well as heritability has been found to be stronger for ADHD hyperactive-impulsive symptoms. My findings did not indicate that prenatal substance use had different effects on ADHD hyperactive-impulsive and inattention symptom

domains. However, lack of evidence may be also affected by scales used for distinguishing ADHD symptom domains, which also needs further investigation.

7.5 FUTURE DIRECTION

7.5.1 Phenotyping of ADHD

Several studies have shown that ADHD symptoms across a population are continuously presented (Larsson et al., 2012), but a large number of studies are still using binary measures to overcome methodological limitations because of skewed distributions in general population-based studies (Burton et al., 2019; Swanson et al., 2012). The Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour Rating Scale (SWAN) has been suggested as a more suitable scale to measure ADHD dimensionally where the scores produce a normal distribution (Swanson et al., 2012). SWAN has been shown to be a good measure also in molecular genetics research for capturing genetic variation across the continuum of ADHD traits, and SWAN enables differentiation of ADHD hyperactive-impulsive and inattention symptom domains (Burton et al., 2019; Greven et al., 2016). Considering that it is possible that prenatal substance use may have somewhat different effects on ADHD hyperactive-impulsive and inattention symptoms, SWAN could be a better scale to further investigate the effects of prenatal substance use on offspring ADHD symptom domains.

Moreover, as discussed in Chapter 6, more detailed phenotyping of ADHD using endophenotypes could be one solution to distinguish ADHD from FASD diagnoses. Several studies have found that executive function deficits are somewhat different in children with ADHD and FASD (Kingdon et al., 2016). One such a study found that children with ADHD and FASD have different sustained attention and inhibition profiles (Kooistra et al., 2010). Another study using neuroimaging techniques found some white-matter pathology in prenatally alcohol exposed children with ADHD compared to ADHD children without prenatal alcohol exposure (O'Neill et al., 2019).

Other aspects to consider in ADHD phenotyping are the change in symptoms across developmental periods, and high comorbidity with other mental health disorders which can also change in different developmental periods (Franke et al., 2018). A study in ALSPAC found 4-class trajectories of ADHD at age 4 to 17 years: low; intermediate; childhood-limited and persistent where the highest genetic loading and comorbidity was observed in the persistent trajectory (Riglin et al., 2016). Another study also identified an ADHD late-onset trajectory that begins in adolescence (Manfro et al., 2019). However, there is an ongoing debate whether late-onset ADHD exists and to what extent it differs from childhood ADHD (Asherson and Agnew-Blais, 2019). Currently, there are few studies which have investigated whether prenatal substance use has different effects on ADHD with comorbid disorders. One such study found that the strongest effect of maternal prenatal smoking was observed on ADHD with comorbid ODD (Joelsson et al., 2016).

In order to gain clarity in these areas, more longitudinal studies with repeated measures which investigate ADHD symptoms with and without comorbidities over the life course, are needed.

7.5.2 Establishing stronger causal inference

Although a combination of negative control and PRS analyses can provide stronger evidence for a causal effect, my PRS analyses were affected by low power. Both PRS analyses (Chapter 5 and 6) and the PheWAS approach (Chapter 4) do not formally estimate the causal effect. Therefore, future studies should use more sophisticated methods in bigger samples to further investigate whether a true causal effect exists.

7.5.2.1 Natural experiments and quasi-experimental designs

Quasi-experimental designs, such as negative control, sibling comparison, as well as twin and other genetically sensitive designs can all contribute to a better and stronger causal inference (Rutter, 2007).

Also, natural experiments are useful approaches in general population studies. For example, universal experiences could be applied to caffeine exposure. The current guidelines in the UK advise pregnant women to limit their caffeine intake during pregnancy to less than 200mg a day. However, before 2008 the upper limit of caffeine intake in pregnancy was advised as 300mg a day (Miles and Foxen, 2009). This change over time could provide an opportunity to investigate whether children born to mothers who could consume more caffeine during pregnancy experienced more developmental difficulties compared to children whose mothers were recommended to drink less caffeine. Although this type of experiment will not solve the problem of unmeasured confounding, it can still provide a hypothesis for a potential causal effect.

Another example of how quasi-experimental designs could be useful to disentangle maternal prenatal substance use effects from postnatal effects, is to use genetically sensitive designs. For instance, a study on cocaine exposure conducted in children reared by their biological mothers and adoptive parents concluded that children raised by adoptive parents or biological mothers did not differ substantially in their mean IQ indicating that observed lower IQ is because of the actual prenatal cocaine exposure and not due to the postnatal environment (Singer et al., 2004). This type of study design could also be used to disentangle prenatal effects from postnatal effects on offspring ADHD symptoms in other substances. Although given the high comorbidity between smoking, alcohol and caffeine use, it may still be difficult to separate specific effects of each substance on the outcome.

7.5.2.2 Two-Sample Mendelian Randomization (MR)

Two-sample MR could be used to estimate the causal effect of prenatal exposures on offspring health outcomes. Two-sample MR has been established to overcome limitations due to the Winner's curse in one-sample MR and increase power to detect a potential causal effect. The main principle of two-sample MR is that the SNP-exposure association is measured in one sample and the SNP-outcome association is measured in another sample (Lawlor, 2016). Although not all the MR assumptions can be

tested in two-sample MR either, methods have been developed to test for pleiotropy. For example, the inverse variance weighted method assumes that all genetic variants are valid instruments and there is no pleiotropy. Alternatively, MR Egger allows all genetic variants to violate MR assumptions and the weighted median assumes that majority of the genetic variants satisfy MR assumptions (Bowden et al., 2017; Burgess and Thompson, 2017; Slob and Burgess, 2020).

However, to increase the power to detect a potential causal effect establishment of large-scale consortia are needed to perform two-sample MR studies in the context of prenatal exposures and intergenerational research (Evans et al., 2019).

7.5.2.3 Multivariable MR

As an extension of the one- and two-sample MR approaches, multivariable MR enables the use of multiple genetic variants associated with several risk factors simultaneously to estimate the causal effect on the outcome (Sanderson et al., 2019). Considering high comorbidity between smoking, alcohol and caffeine use, multivariable MR would enable researchers to estimate direct causal effects of each exposure on the outcome independent of the others. Multivariable MR can be used with individual level data as well as in two sample settings. Similarly to two-sample MR, sensitivity analyses can be performed to test for pleiotropy (Rees et al., 2017), but also bigger sample sizes are needed than currently available to use this method in intergenerational research and on prenatal exposures.

7.5.2.4 Transmitted and Non-Transmitted Alleles

Alternatively, in the situation where the impact of genetic transmission on the child health outcomes is likely and paternal genetic data is limited, it is also possible to investigate causal effects by separating maternal transmitted and non-transmitted alleles. Conducting MR analyses using maternal non-transmitted alleles will reduce collider bias if paternal genetic data is not available and can provide more evidence for a causal effect (Lawlor et al., 2017). One such a study investigating offspring adiposity found no support for a causal effect of maternal BMI on offspring BMI

when maternal non-transmitted alleles were used in MR analysis (Richmond et al., 2017).
However, similarly to other MR approaches, large sample sizes are needed to be sufficiently powered to detect a potential causal effect when using non-transmitted alleles.

Furthermore, non-transmitted alleles could be used to examine genetic nurturing effects. For example, it has been found that PRS for educational attainment based on non-transmitted alleles was not associated with children's ADHD symptoms indicating that genetic nurturing related to parental educational characteristics was not relevant in ADHD (de Zeeuw et al., 2020). However, genetic nurturing effects may differ when using parental non-transmitted alleles based on substance use behaviours. A recent study based on MoBa did not find evidence for genetic nurturing effects between maternal prenatal smoking and child ADHD symptoms, but more research is needed for other exposures (Pingault et al., 2021).

7.5.2.5 Structural Equation Models (SEM)

Additionally, structural equation models (SEM) have been developed to investigate intergenerational associations by taking into account both genetic and environmental influences, as well as genetic transmission between parents and offspring (Hannigan et al., 2018; McAdams et al., 2018). A study in MoBa using SEM have found some evidence that maternal prenatal depression can have a direct effect on offspring ADHD symptoms after accounting for genetic transmission (Eilertsen et al., 2020). This model could be also applied to further investigate whether maternal prenatal substance use can have a direct effect on offspring ADHD after accounting for genetic confounding.

7.5.3 Evocative effects

It has been suggested that offspring externalising problems may be a result of gene-environment correlations where parental behaviour is a response to children's genetically influenced behaviour (*evocative effects*) indicating that the relationship between negative parenting behaviour and offspring

externalising problems is bidirectional (Marceau et al., 2013). Furthermore, it has been found that children who were genetically predisposed to ADHD related impulsive behaviour experienced more hostile parenting by their genetically unrelated mothers which also predicted child ADHD symptoms at later age (Harold et al., 2013). Another study that examined evocative effects by using PRS to control for passive gene-environment correlation between parents and offspring found that children's genetic predisposition for behavioural difficulties was associated with poorer parental monitoring via children's impulsivity which also contributed to affiliation with substance-using peers in adolescence (Elam et al., 2017). Therefore, it is plausible that offspring ADHD symptoms may have an effect on maternal substance use which also influences offspring ADHD via parenting behaviour.

7.6 THESIS CONCLUSIONS

The main aim of this thesis was to investigate whether there is a causal effect of maternal smoking, alcohol, or caffeine consumption during pregnancy on ADHD risk in offspring. I used both observational and genetic analyses and triangulated my findings across different methods applied in this thesis. Taken together, I did not find strong evidence to support a causal effect of maternal prenatal substance use on offspring ADHD risk. My findings on prenatal smoking and caffeine exposure suggest that a causal effect of these exposures on offspring ADHD is unlikely, in line with previous studies on these substances. The results do not differ according to method of ADHD assessment (i.e., based on diagnosis or symptom score). My findings on prenatal alcohol exposure are less conclusive, when considered in the context of the wider literature. While my analyses do not support a causal effect, other studies have found some evidence for a causal effect of prenatal alcohol exposure on offspring ADHD, but there remains the possibility that ADHD characteristics/behaviours that overlap with FASD are behind these observations.

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APPENDICES

Appendix 2.1. Search performed in Medline (Ovid platform) including relevant MeSH Terms

1. disruptive, impulse control, and conduct disorders"/ or "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/ or child behavior disorders/ - MeSH Terms
2. Child Behavior Disorders/ - MeSH Terms
3. Impulsive Behavior/ - MeSH Terms
4. Problem Behavior/ - MeSH Terms
5. attention deficit disorder.tw
6. hyperactiv*.tw
7. impulsiv*.tw
8. ADHD.tw
9. attention deficit hyperactivity.tw
10. externali?ing.tw
11. conduct disorder.tw
12. behavio* disorders.tw
13. behavio* problem*.tw
14. disruptive behavio*.tw
15. oppositional defiant disorder.tw
16. ALCOHOLS/ - MeSH Terms
17. DRINKING BEHAVIOR/ or ALCOHOL DRINKING/ or DRINKING/ or BINGE DRINKING/ - MeSH Terms
18. TOBACCO USE"/ or TOBACCO/ or TOBACCO SMOKING – MeSH Terms
19. CAFFEINE/ - MeSH Terms
20. COFFEE/ - MeSH Terms
21. TEA/ - MeSH Terms
22. Energy Drinks/ - MeSH Terms
23. Ethanol – MeSH Terms
24. Taurine – MeSH Terms
25. alcohol*.tw
26. tobacco.tw
27. caffein*.tw
28. drink*.tw
29. ethanol.tw
30. smoking.tw
31. cigarette*.tw
32. nicotine.tw
33. coffee.tw
34. tea.tw
35. energy.drink*.tw
36. taurine.tw
37. Pregnancy trimesters – MeSH Terms
38. Pregnancy – MeSH Terms
39. PREGNANCY TRIMESTER, SECOND/ or PREGNANCY TRIMESTER, FIRST/ or PREGNANCY TRIMESTER, THIRD/ - MeSH Terms
40. Pregnan*.tw
41. Perinatal*.tw
42. Prenatal*.tw

43. Intrauterine*.tw
44. Utero.tw
45. F?etal.tw
46. Gestation.tw
47. Trimester.tw

Appendix 2.2. Risk of bias assessment

Newcastle Ottawa Scale for cohort studies

Item	Points
Selection	
1) Representativeness of the exposed cohort	1 point – cohort is representative of the average pregnant woman in the community 0 points – cohort is based on selected group or not representative or no description of the cohort of interest
2) Selection of the non-exposed cohort	1 point – drawn from the same community as exposed cohort 0 points – drawn from a different source or no description provided
3) Ascertainment of exposure	1 point – exposure assessed prospectively or assigned from the medical record 0 points – retrospective assessment or may be at risk for recall bias or no description
4) Demonstration that outcome of interest was not present at start of study	1 point – yes 0 points – no
Comparability	
5) Comparability of cohorts on the basis of the design or analysis	1 point – study controls for potential confounder other than sociodemographic factors (such as social class, education, maternal age and ethnicity, child gender) 2 points – study controls for any other additional factor 0 points – no confounders included, or study does not control for sociodemographic factors
Outcome	
6) Assessment of outcome	1 point – record linkage or assessment based on multiple sources and/or evaluation by clinician 0 points - self-report or no reference to records or no assessment by clinician
7) Was follow-up long enough for outcome to occur	1 point – child age at least 6-7 years or 50% of the sample is older than 6 years 0 points – child age less than 6 years or >50% of the sample is younger than 6 years
8) Adequacy of follow up of cohorts	1 point – complete follow up or loss to follow-up is <50% 0 points - >50% of the sample lost to follow up or no information provided

Newcastle Ottawa Scale for case-control studies

Item	Points
Selection	
1) Is the case definition adequate?	1 point – independent validation (record linkage or using multiple sources and clinical assessment) 0 points – based on self-reports with no clinical validation or no description
2) Representativeness of the cases	1 point – eligible cases over a defined period of time, in a defined catchment area or clearly defined group 0 points – potential for selection bias or not stated
3) Selection of controls	1 point – same community as cases 0 points – hospital controls or not representing controls without mental health problems
4) Definition of controls	1 point – no history of disease (endpoint) 0 points – not meeting criteria for endpoint or no description
Comparability	
5) Comparability of cases and controls on the basis of the design or analysis	1 point – study controls for potential confounder other than sociodemographic factors (such as social class, education, maternal age and ethnicity, child gender) 2 points – study controls for any other additional factor 0 points – no confounders included, or study does not control for sociodemographic factors
Exposure	
6) Ascertainment of exposure	1 point – secure record, prospective measure or structured interview blind to case/control status 0 points – assessment not blinded to case/control status or retrospective self-report or may be at risk for recall bias
7) Same method of ascertainment for cases and controls	1 point – yes 0 points – no
8) Non-response rate	1 point – same rate for both groups 0 points – rate different or non-respondents described

Appendix 2.3. Risk of bias assessment scores based on NOS scale of cohort, longitudinal and cross-sectional studies

Study	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Total
Smoking									
Ball et al., 2010	1	1	0	1	1	0	1	0	5
Gustavson et al., 2017	1	1	1	1	2	1	1	1	9
Langley et al., 2012	1	1	1	1	1	0	1	0	6
Obel et al., 2011	1	1	1	1	1	1	1	1	8
Obel et al., 2016	1	1	1	1	0	1	1	1	7
Skoglund et al., 2014	1	1	1	1	0	1	1	1	7
Zhu et al., 2014	1	1	1	1	2	1	1	1	9
Lehn et al., 2007*	1	1	1	1	1	0	1	1	7
Lindblad et al., 2010	1	1	1	1	2	1	1	1	9
Braun et al., 2006	1	1	0	0	1	0	1	0	4
Wakschlag et al., 1997	0	1	0	0	2	1	1	1	6
Talati et al., 2016*	0	1	0	0	0	1	1	1	4
Braun et al., 2008	1	1	0	0	0	0	1	1	4
Ellis et al., 2012	1	1	0	0	2	0	0	1	5
Nigg et al., 2007	1	1	0	0	1	0	1	1	5
Talati et al., 2017	0	1	0	1	0	1	1	1	5
Weissman et al., 1999	0	1	0	0	0	1	1	1	4
Nomura et al., 2010	0	0	0	0	2	1	0	0	3
Neuman et al., 2007	1	1	0	1	2	0	1	0	6
Koshy et al., 2011	0	1	0	0	0	0	1	0	2
Sciberras et al., 2011	1	1	0	0	1	0	1	1	5
Froehlich et al., 2009	1	1	0	0	1	0	1	0	4
Knopik et al., 2006	1	1	0	0	0	1	1	0	4
Alcohol									
Eilertsen et al., 2017	1	1	1	1	1	1	0	0	6
Larkby et al., 2011	1	1	1	1	2	0	1	1	8
Caffeine									
Del-Ponte et al., 2016	1	1	0	1	2	1	1	1	8
Linnet et al., 2008	1	1	1	1	2	1	1	1	9
Smoking and Alcohol									
Fergusson et al., 1998	1	1	1	1	2	0	1	1	8
Pohlabeln et al., 2017	0	1	0	0	2	0	1	1	5
Sagiv et al., 2013	1	1	1	1	2	1	1	1	9
Schmitt et al., 2012	1	1	0	0	2	0	1	0	5
Whitbeck et al., 2009	0	1	0	0	0	0	1	0	2
Knopik et al., 2005	1	1	0	0	1	0	1	1	5
Smoking, alcohol and caffeine									
Russell et al., 2015	0	1	0	0	0	0	1	0	2

Appendix 2.4. Risk of bias assessment scores based on NOS scale of case-control studies

Study	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Total
Smoking									
Biederman et al., 2009	1	1	0	1	2	0	1	0	6
Gard et al., 2010	0	0	0	0	1	0	1	0	2
Gustaffson and Kallen, 2010	1	1	1	1	0	1	1	1	7
Joelsson et al., 2016	1	1	1	1	2	1	1	1	9
Linnet et al., 2005	1	1	1	1	2	1	1	1	9
Milberger et al., 1996	1	1	0	1	1	0	1	0	5
Milberger et al., 1998	1	1	0	1	1	0	1	0	5
Motlagh et al., 2010	1	1	1	1	0	0	0	0	4
Schmitz et al., 2006	1	1	1	1	2	0	1	1	8
Silva et al., 2014	1	1	1	1	2	0	1	1	8
Todd et al., 2007	0	1	1	1	1	0	1	0	5
Yoshimasu et al., 2009	1	1	0	1	2	0	1	1	7
Altink et al., 2009	1	1	1	1	2	0	1	0	7
Altink et al., 2008	1	1	1	1	0	0	1	0	5
Arnold et al., 2005	1	1	1	1	2	0	1	0	7
Biederman et al., 2017	1	1	0	1	0	0	1	0	4
Oerlemans et al., 2016	1	1	1	1	0	0	1	0	5
Smoking and Alcohol									
Ketzer et al., 2012	1	1	1	1	1	0	1	0	6
Mick et al., 2002	1	1	0	1	1	0	1	0	5
Pineda et al., 2007	1	1	1	1	0	0	1	1	6
Wiggs et al., 2016	1	1	1	1	1	0	1	0	6
Alcohol and caffeine									
Kim et al., 2009	0	1	1	1	0	0	1	0	4

Appendix 2.5. List of studies excluded

	Author	Year	Title	Exclusion reason
1.	Brookes et al.	2006	A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy	no comparison/control group
2.	Freitag et al.	2012	Biological and psychosocial environmental risk factors influence symptom severity and psychiatric comorbidity in children with ADHD	no comparison/control group
3.	Brookes et al.	2006	Association of Fatty Acid Desaturase Genes with Attention-Deficit/Hyperactivity Disorder	no comparison/control group
4.	Langley et al.	2007	Effects of low birth weight, maternal smoking in pregnancy and social class on the phenotypic manifestation of Attention Deficit Hyperactivity Disorder and associated antisocial behaviour: investigation in a clinical sample	no comparison/control group
5.	Langley et al.	2008	Testing for gene x environment interaction effects in attention deficit hyperactivity disorder and associated antisocial behavior	no comparison/control group
6.	Thakur et al.	2012	Comprehensive Phenotype/Genotype Analyses of the Norepinephrine Transporter Gene (SLC6A2) in ADHD: Relation to Maternal Smoking during Pregnancy	no comparison/control group
7.	Thakur et al.	2013	Maternal smoking during pregnancy and ADHD: A comprehensive clinical and neurocognitive characterization	no comparison/control group
8.	Biederman et al.	2012	Does exposure to maternal smoking during pregnancy affect the clinical features of ADHD? Results from a controlled study	no comparison/control group
9.	Bhatara et al.	2006	Association of attention deficit hyperactivity disorder and gestational alcohol exposure: An exploratory study	no comparison/control group
10.	Xu et al.	2010	Racial differences in the effects of postnatal environmental tobacco smoke on neurodevelopment	wrong exposure
11.	Mulligan et al.	2013	Home environment: association with hyperactivity/impulsivity in children with ADHD and their non-ADHD siblings	wrong exposure

12.	Naeye and Peters	1984	Mental development of children whose mothers smoked during pregnancy	wrong outcome
13.	Holz et al.	2014	Effect of Prenatal Exposure to Tobacco Smoke on Inhibitory Control Neuroimaging Results from a 25-Year Prospective Study	wrong outcome
14.	Martel and Roberts	2014	Prenatal testosterone increases sensitivity to prenatal stressors in males with disruptive behavior disorders	wrong exposure
15.	Wakschlag and Keenan	2001	Clinical significance and correlates of disruptive behavior in environmentally at-risk preschoolers	don' t meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
16.	Sengupta et al.	2015	Parental psychopathology in families of children with attention-deficit/hyperactivity disorder and exposed to maternal smoking during pregnancy	wrong outcome
17.	Mick et al.	2002	Impact of low birth weight on attention-deficit hyperactivity disorder	wrong exposure
18.	Grabell and Olson	2010	Executive functioning as a mediating factor of prenatal alcohol exposure and externalizing problems in preschool children	conference/meeting abstract
19.	Schmitz et al.	2017	Pre- and perinatal risk factors in autism spectrum disorder and attention deficit/hyperactivity disorder	not English language
20.	Willoughby et al.	2012	Parent-Reported Attention Deficit/Hyperactivity Symptomatology in Preschool-Aged Children: Factor Structure, Developmental Change, and Early Risk Factors	no comparison/control group
21.	Wiliams et al.	1998	Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study	wrong outcome
22.	Whitaker et al.	2011	Serial pediatric symptom checklist screening in children with prenatal drug exposure	wrong exposure
23.	Whitaker et al.	2006	Food insecurity and the risks of depression and anxiety in mothers and behavior problems in their preschool-aged children	wrong exposure
24.	Way and Rojahn	2012	Psycho-social characteristics of children with prenatal alcohol exposure, compared to children with Down syndrome and typical children	wrong outcome

25.	Twardella et al.	2010	Exposure to secondhand tobacco smoke and child behaviour - results from a cross-sectional study among preschool children in Bavaria	wrong exposure
26.	Vuijk et al.	2006	Prenatal smoking predicts non-responsiveness to an intervention targeting attention-deficit/hyperactivity symptoms in elementary schoolchildren	retracted
27.	Van Den Berg and Marcoen	2004	High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds	wrong exposure
28.	Todd and Neuman	2007	Gene-environment interactions in the development of combined type ADHD: evidence for a synapse-based model	duplicate
29.	Tiesler and Heinrich	2014	Prenatal nicotine exposure and child behavioural problems	review
30.	Teramoto et al.	2005	Problematic behaviours of 3-year-old children in Japan: Relationship with socioeconomic and family backgrounds	externalising disorder not specified
31.	Tearne et al.	2015	The association between prenatal environment and children's mental health trajectories from 2 to 14 years	externalising disorder not specified
32.	Höök et al.	2006	Prenatal and postnatal maternal smoking as risk factors for preschool children's mental health	externalising disorder not specified
33.	Schonfeld et al.	2005	Moral maturity and delinquency after prenatal alcohol exposure	FAS sample
34.	Roza et al.	2009	Maternal smoking during pregnancy and child behaviour problems: the Generation R Study	externalising disorder not specified
35.	Schlotz et al.	2010	Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring	wrong exposure
36.	Salom et al.	2015	Familial factors associated with development of alcohol and mental health comorbidity	wrong exposure (not measured during pregnancy)
37.	Salom et al.	2016	Predictors of comorbid polysubstance use and mental health disorders in young adults-a latent class analysis	wrong outcome
38.	Ruchkin et al.	2008	Developmental pathway modeling in considering behavior problems in young Russian children	externalising disorder not specified

39.	Pauli-Rott et al.	2017	Psychosocial risk factors underlie the link between attention deficit hyperactivity symptoms and overweight at school entry	wrong exposure
40.	Paley et al.	2005	Prenatal Alcohol Exposure, Child Externalizing Behavior, and Maternal Stress	externalising disorder not specified
41.	Oulhote and Bouchard	2013	Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children	wrong exposure
42.	Olson et al.	1992	Prenatal exposure to alcohol and school problems in late childhood: A longitudinal prospective study	externalising disorder not specified
43.	Robinson et al.	2010	Low-moderate prenatal alcohol exposure and risk to child behavioural development: A prospective cohort study	externalising disorder not specified
44.	Robinson et al.	2008	Pre- and postnatal influences on preschool mental health: A large-scale cohort study	externalising disorder not specified
45.	Robinson et al.	2010	Smoking cessation in pregnancy and the risk of child behavioural problems: A longitudinal prospective cohort study	externalising disorder not specified
46.	Pineda et al.	2003	Perinatal factors associated with attention deficit/hyperactivity diagnosis in Colombian Paisa children]	not English language
47.	Pfinder et al.	2014	Impact of Moderate Prenatal Alcohol Exposure on Problem Behaviors in Preschool and School Children	duplicate
48.	Petkovsek et al.	2014	Prenatal smoking and genetic risk: Examining the childhood origins of externalizing behavioral problems	externalising disorder not specified
49.	Oćallaghan et al.	1997	Obstetric and perinatal factors as predictors of child behaviour at 5 years	externalising disorder not specified
50.	O'Brien et al.	2013	Do dopamine gene variants and prenatal smoking interactively predict youth externalizing behavior?	no comparison/control group
51.	Niemela et al.	2016	Maternal smoking during pregnancy and offpsring's psychiatric morbidity in early adulthood. Findings from the Finnish Family Competence Birth Cohort Study	conference/meeting abstract
52.	Niclasen et al.	2012	Prenatal exposure to alcohol and neurobehavioural development at age seven	conference/meeting abstract
53.	Najman et al.	2000	Preschool children and behaviour problems - A prospective study	externalising disorder not specified

54.	Glass et al.	2014	Correspondence of parent report and laboratory measures of inattention and hyperactivity in children with heavy prenatal alcohol exposure	FAS sample
55.	Fryer et al.	2007	Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure	FAS sample
56.	Mina et al.	2017	Prenatal exposure to very severe maternal obesity is associated with adverse neuropsychiatric outcomes in children	wrong exposure
57.	Melchior et al.	2012	Food Insecurity and Children's Mental Health: A Prospective Birth Cohort Study	wrong exposure
58.	Mullen et al.	2017	Effects of prenatal alcohol exposure on child behaviour outcomes at age five: Lifeways Cross-Generational Cohort Study	conference/meeting abstract
59.	Monshouwer et al	2011	Prenatal smoking exposure and the risk of behavioral problems and substance use in adolescence: The TRAILS study	externalising disorder not specified
60.	Minnes et al.	2010	The effects of prenatal cocaine exposure on problem behavior in children 4-10 years	wrong exposure
61.	Momany et al.	2017	Sex moderates the impact of birth weight on child externalizing psychopathology	wrong exposure
62.	Milberger et al.	1996	Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children?	duplicate
63.	MacKinnon et al.	2018	The Association Between Prenatal Stress and Externalizing Symptoms in Childhood: Evidence From the Avon Longitudinal Study of Parents and Children	wrong exposure
64.	Lukkari et al.	2012	Exposure to Obstetric Complications in Relation to Subsequent Psychiatric Disorders of Adolescent Inpatients: Specific Focus on Gender Differences	wrong exposure
65.	McLaughlin et al.	2011	Caregiver and self-report of mental health symptoms in 9-year old children with prenatal cocaine exposure	wrong exposure
66.	McCrory et al.	2012	Prenatal exposure to maternal smoking and childhood behavioural problems: A quasi-experimental approach	externalising disorder not specified

67.	Maughan et al.	2004	Prenatal smoking and early childhood conduct problems: Testing genetic and environmental explanations of the association	don't meet outcome criteria (maternal and teacher reported measure of conduct disorder and delinquent behaviour symptoms)
68.	Marceau et al.	2018	Within-Family Effects of Smoking during Pregnancy on ADHD: the Importance of Phenotype	don't meet outcome criteria (maternal reported ADHD symptoms)
69.	Linnet et al.	2003	Maternal Lifestyle Factors in Pregnancy Risk of Attention Deficit Hyperactivity Disorder and Associated Behaviors: Review of the Current Evidence	review
70.	Langley et al.	2005	Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review	review
71.	Coles et al.	1997	A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder	FAS sample
72.	Walthall et al.	2008	A comparison of psychopathology in children with and without prenatal alcohol exposure	FAS sample
73.	Neiderhiser et al.	2016	Estimating the Roles of Genetic Risk, Perinatal Risk, and Marital Hostility on Early Childhood Adjustment: Medical Records and Self-Reports	externalising disorder not specified
74.	Max et al.	2013	Attention deficit hyperactivity disorder among children exposed to secondhand smoke: A logistic regression analysis of secondary data	wrong exposure
75.	Marin-Mendez et al.	2015	Environmental factors associated with suspected ADHD in preschoolers using a screening tool (ADHD-RS-IV-P)	wrong exposure (not measured in pregnancy)
76.	Maat et al.	2017	Attention-deficit hyperactivity disorder (adhd) symptoms in children adopted from poland and their atypical association patterns: A bayesian approach	no exposure-outcome association measured
77.	Linnet al.	2006	Gestational age, birth weight, and the risk of hyperkinetic disorder	wrong exposure

78.	LaGasse et al.	2012	Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age	wrong exposure
79.	Lewis et al.	2016	Prospective Memory Impairment in Children with Prenatal Alcohol Exposure	FAS sample
80.	Lahti et al.	2006	Small body size at birth and behavioural symptoms of ADHD in children aged five to six years	wrong exposure
81.	Maatta et al.	2017	Maternal Smoking During Pregnancy Is Associated With Offspring's Musculoskeletal Pain in Adolescence: Structural Equation Modeling	wrong outcome
82.	Li et al.	1996	Study of child's behavior problem in logistic regression analysis	not English language
83.	Langley et al.	2010	Maternal and paternal smoking during pregnancy and risk for child ADHD: A test for causal associations	conference/meeting abstract
84.	Kukla et al.	2006	Smoking of mothers during pregnancy in relation to mental and motoric development disorders in 4- and 5-year-old children. The elspac study results	not English language
85.	Wakschlag et al.	2006	Elucidating early mechanisms of developmental psychopathology: The case of prenatal smoking and disruptive behavior	wrong outcome
86.	Leung et al.	2015	Early second-hand smoke exposure and child and adolescent mental health: Evidence from Hong Kong's 'Children of 1997' birth cohort	wrong exposure
87.	Silva et al.	2015	Comorbidities of Attention Deficit Hyperactivity Disorder: Pregnancy Risk Factors and Parent Mental Health	combined outcome
88.	Nanson and Hiscock	1990	Attention deficits in children exposed to alcohol prenatally	FAS sample
89.	Marino et al.	2010	Association of maternal lifestyle factors in pregnancy and birth weight with attention-deficit/hyperactivity disorder in a population of Italian children	conference/meeting abstract
90.	Rasmussen et al.	2011	An evaluation of social skills in children with and without prenatal alcohol exposure	FAS sample
91.	Tervo et al.	2017	A Prospective 30-Year Follow-Up of ADHD Associated With Perinatal Risks	wrong exposure

92.	Wiggs et al.	2017	A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement	wrong exposure
93.	Knudsen et al.	2014	Maternal pre-pregnancy risk drinking and toddler behavior problems: the Norwegian Mother and Child Cohort Study	externalising disorder not specified
94.	Knopik et al.	2010	Smoking during pregnancy, maternal xenobiotic metabolism genes, and child externalizing behavior: A case-crossover design	conference/meeting abstract
95.	Knopik et al.	2009	Maternal smoking during pregnancy and child outcomes: Real or spurious effect?	review
96.	Knopik et al.	2015	Smoking during pregnancy and ADHD risk: A genetically-informed, multiple-rater approach	duplicate
97.	Keyes et al.	2012	Associations of prenatal maternal smoking with offspring hyperactivity: Causal or confounded?	duplicate
98.	Kesmodel et al.	2010	Lifestyle during pregnancy: neurodevelopmental effects at 5 years of age. The design and implementation of a prospective follow-up study	wrong outcome
99.	Katwan et al.	2011	Childhood behavioural and developmental disorders: association with maternal alcohol consumption in Cape Town, South Africa	externalising disorder not specified
100.	Kahn et al.	2005	Intergenerational health disparities: Socioeconomic status, women's health conditions, and child behavior problems	externalising disorder not specified
101.	Johnson et al.	2001	Moderate alcohol and tobacco use during pregnancy and child behavior outcomes	don't meet outcome criteria (maternal reported measure of conduct disorder)
102.	Jaspers et al.	2012	Trajectories of psychosocial problems in adolescents predicted by findings from early well-child assessments	externalising disorder not specified
103.	Jaspers et al.	2010	Early findings of preventive child healthcare professionals predict psychosocial problems in preadolescence: The TRAILS study	externalising disorder not specified

104.	Jacka et al.	2013	Maternal and early postnatal nutrition and mental health of offspring by age 5 years: A prospective cohort study	wrong exposure
105.	Irner et al.	2014	Cognitive, emotional and social development in adolescents born to substance using women	wrong exposure
106.	Holz et al.	2015	The long-term impact of early life poverty on orbitofrontal cortex volume in adulthood: Results from a prospective study over 25 years	wrong exposure
107.	Infante et al.	2015	Objective assessment of ADHD core symptoms in children with heavy prenatal alcohol exposure	FAS sample
108.	Huizink et al.	2006	Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring	review
109.	Huang et al.	2018	Maternal smoking and attention-deficit/hyperactivity disorder in offspring: A meta-analysis	review/meta-analysis
110.	Henry et al.	2007	Neurobiology and neurodevelopmental impact of childhood traumatic stress and prenatal alcohol exposure	FAS sample
111.	Habek et al.	2011	Adverse pregnancy outcomes and long-term morbidity after early fetal hypokinesia in maternal smoking pregnancies	no exposure-outcome association measured
112.	Gray et al.	2004	Prevalence, stability, and predictors of clinically significant behavior problems in low birth weight children at 3, 5, and 8 years of age	externalising disorder not specified
113.	Hay et al.	2008	Antepartum and postpartum exposure to maternal depression: Different effects on different adolescent outcomes	wrong exposure
114.	deMaat et al.	2018	Attention-Deficit Hyperactivity Disorder (ADHD) Symptoms in Children Adopted from Poland and their Atypical Association Patterns: a Bayesian Approach	duplicate
115.	Burden et al.	2010	An event-related potential study of response inhibition in ADHD with and without prenatal alcohol exposure	wrong outcome
116.	Gronimus et al.	2009	Maternal alcohol consumption	review
117.	Griesler et al.	1998	Maternal smoking in pregnancy, child behavior problems, and adolescent smoking	externalising disorder not specified

118.	Graham et al.	2013	Prenatal Alcohol Exposure, Attention-Deficit/Hyperactivity Disorder, and Sluggish Cognitive Tempo	FAS sample
119.	Goodwin et al.	2013	Maternal nicotine dependence and prenatal smoking and their association with mental disorders among offspring from the community	conference/meeting abstract
120.	Goldman et al.	2011	Direct and modifying influences of selected risk factors on children's pre-adoption functioning and post-adoption adjustment	wrong outcome
121.	Glass et al.	2013	Neuropsychological deficits associated with heavy prenatal alcohol exposure are not exacerbated by ADHD	FAS sample
122.	Amiri et al.	2012	Pregnancy-related maternal risk factors of attention-deficit hyperactivity disorder: a case-control study	combined exposure (tobacco and alcohol)
123.	Fitzpatrick et al.	2017	Prevalence and profile of Neurodevelopment and Fetal Alcohol Spectrum Disorder (FASD) amongst Australian Aboriginal children living in remote communities	FAS sample
124.	Furtado and Roriz	2016	Inattention and impulsivity associated with prenatal alcohol exposure in a prospective cohort study with 11-years-old Brazilian children	wrong outcome
125.	Furlong et al.	2017	Early life characteristics and neurodevelopmental phenotypes in the mount sinai children's environmental health center	externalising disorder not specified
126.	Froehlich et al.	2011	Update on environmental risk factors for attention-deficit/hyperactivity disorder	review
127.	Flak et al.	2014	The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: A meta-analysis	review/meta-analysis
128.	Finnegan	1981	The effects of narcotics and alcohol on pregnancy and the newborn	review
129.	Erb and Andresen	1981	Hyperactivity: a possible consequence of maternal alcohol consumption	review
130.	Ekblad et al.	2017	Maternal smoking during pregnancy and the risk of psychiatric morbidity in singleton sibling pairs	externalising disorder not specified

131.	Aronson et al.	1997	Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: A follow-up study	FAS sample
132.	Eiden et al.	2011	Child behavior problems among cocaine-exposed toddlers: Indirect and interactive effects	wrong exposure
133.	Camprodon-Rosanas et al.	2017	Sluggish Cognitive Tempo: Sociodemographic, Behavioral, and Clinical Characteristics in a Population of Catalan School Children	wrong outcome
134.	Delaney-Black et al.	1998	Prenatal Coke: What's Behind the Smoke?: Prenatal Cocaine/Alcohol Exposure and School-Age Outcomes: The SCHOO-BE Experiencea	no exposure-outcome association measured
135.	Button et al.	2007	The relationship of maternal smoking to psychological problems in the offspring	review
136.	Boseck et al.	2015	Cognitive and Adaptive Skill Profile Differences in Children With Attention-Deficit Hyperactivity Disorder With and Without Comorbid Fetal Alcohol Spectrum Disorder	FAS sample
137.	Biederman et al.	2014	Is ADHD a risk for posttraumatic stress disorder (PTSD)? Results from a large longitudinal study of referred children with and without ADHD	wrong outcome
138.	Boutwell et al.	2011	Prenatal exposure to cigarette smoke and childhood externalizing behavioral problems: A propensity score matching approach	externalising disorder not specified
139.	Boutwell and Beaver	2010	Maternal cigarette smoking during pregnancy and offspring externalizing behavioral problems: A propensity score matching analysis	externalising disorder not specified
140.	Bor et al.	1997	The relationship between low family income and psychological disturbance in young children: An Australian longitudinal study	externalising disorder not specified
141.	Beal et al.	2015	Associations between the prenatal environment and cardiovascular risk factors in adolescent girls: Internalizing and externalizing behavior symptoms as mediators	wrong outcome

142.	Basgul et al.	2011	Frequency and correlates of psychiatric disorders in early childhood: a study of population and clinical samples in Turkey	no exposure-outcome association measured
143.	Barr et al.	2006	Binge Drinking During Pregnancy as a Predictor of Psychiatric Disorders on the Structured Clinical Interview for DSM-IV in Young Adult Offspring	wrong outcome
144.	Bailey et al.	2005	Gender and alcohol moderate prenatal cocaine effects on teacher-report of child behavior	wrong exposure
145.	Bada et al.	2007	Impact of prenatal cocaine exposure on child behavior problems through school age	externalising disorder not specified
146.	Autti-Ramo	2000	Twelve-year follow-up of children exposed to alcohol in utero	FAS sample
147.	Ashford et al.	2008	Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence	don't meet outcome criteria (maternal reported ADHD symptoms)
148.	Arbuckle et al.	2016	Bisphenol A, phthalates and lead and learning and behavioral problems in Canadian children 6-11 years of age: CHMS 2007-2009	wrong exposure
149.	Yao	2017	Mother Smoking During Pregnancy and ADHD in Children	conference/meeting abstract
150.	Gaysina et al.	2013	Prenatal active or passive tobacco smoke exposure and the risk of child externalising problems: Evidence from a genetically-sensitive research design	conference/meeting abstract
151.	Gaysina et al.	2012	Maternal smoking during pregnancy and offspring conduct problems: The evidence for the association using genetically-sensitive designs	conference/meeting abstract
152.	Fago	2013	Impact of prenatal alcohol exposure and pre-adoption placement on school-age functioning of intercountry-adopted children	dissertation
153.	Bidwell et al.	2015	A propensity scoring approach to characterizing the effects of maternal smoking during pregnancy on initial responses to tobacco and alcohol in adolescents	conference/meeting abstract

154.	Baler et al.	2008	Is fetal brain monoamine oxidase inhibition the missing link between maternal smoking and conduct disorders?	review
155.	Wolke et al.	2011	The impact of light drinking in pregnancy on children's behavioural and cognitive development	conference/meeting abstract
156.	Fried et al.	1995	Prenatal exposure to marihuana and tobacco during infancy, early and middle childhood: effects and an attempt at synthesis	conference/meeting abstract
157.	Freitag et al.	2015	Pre-and perinatal risk factors in attention-deficit/ hyperactivity disorder and autism spectrum disorders	conference/meeting abstract
158.	Fitzpatrick and Pagani	2011	Compelling evidence that child impulsivity in fourth grade is predicted by maternal smoking during pregnancy	conference/meeting abstract
159.	Evrensel et al.	2015	Rate of perinatal nicotine exposure in children with the diagnosis of Attention Deficit Hyperactivity Disorder	conference/meeting abstract
160.	Estabrook et al.	2014	The importance of reliable longitudinal measurement in the assessment of prenatal smoking and its relation to youth externalizing behavior	conference/meeting abstract
161.	Enoch et al.	2014	A longitudinal study in mothers and firstborn children of genetic and environmental influences on externalizing and internalizing disorders across development	conference/meeting abstract
162.	Enoch et al.	2015	A prospective cohort study of influences on internalizing and externalizing behaviors across childhood	conference/meeting abstract
163.	Dodge et al.	2010	Protective effects of the alcohol dehydrogenase-adh1b*3 allele in adolescents exposed to alcohol during pregnancy	conference/meeting abstract
164.	Coles et al.	2014	Prenatal tobacco exposure and behavior regulation at 24 months: Child language and maternal psychological symptoms as moderators	conference/meeting abstract
165.	Brookes et al.	2005	A common haplotype of the dopamine transporter gene is associated with attention deficit hyperactivity disorder and interacts with prenatal exposure to alcohol	conference/meeting abstract

166.	Bilgec et al.	2013	Possible prenatal and genetic factors in the etiology of attention deficit hyperactivity disorder: a Turkish referred sample	conference/meeting abstract
167.	Bazinet etal.	2010	Motor activity and inattention during a sustained attention task in children with heavy prenatal alcohol exposure	conference/meeting abstract
168.	Adnams et al.	2014	Behavior in secondary school learnerswith prenatal alcohol exposure in south Africa	conference/meeting abstract
169.	McIntosh et al.	1995	Utilization of maternal perinatal risk indicators in the differential diagnosis of ADHD and UADD children	no exposure-outcome association measured
170.	Jacobson et al.	2011	Number Processing in Adolescents With Prenatal Alcohol Exposure and ADHD: Differences in the Neurobehavioral Phenotype	wrong outcome
171.	Hayatbakhsh et al.	2011	A longitudinal study of child mental health and problem behaviours at 14years of age following unplanned pregnancy	wrong exposure
172.	Gaysina et al.	2013	Maternal smoking during pregnancy and offspring conduct problems: Evidence from 3 independent genetically sensitive research designs	don't meet outcome criteria (maternal reported conduct disorder symptoms)
173.	Yu et al.	2016	Attention Deficit/Hyperactivity Disorder and Urinary Nonylphenol Levels: A Case-Control Study in Taiwanese Children	wrong exposure
174.	Gutvirtz et al.	2018	Maternal smoking and long-term neurological morbidity of the offspring	wrong outcome
175.	Wakschlag and Hans	2002	Maternal smoking during pregnancy and conduct problems in high-risk youth: A developmental framework	don't meet outcome criteria (maternal reported conduct disorder symptoms)
176.	Ware et al.	2013	The effects of prenatal alcohol exposure and attention-deficit/hyperactivity disorder on psychopathology and behavior	FAS sample
177.	Galera et al.	2011	Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years	don't meet outcome criteria (maternal reported ADHD symptoms)

178.	Wasserman et al.	2001	Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
179.	Thapar et al.	2009	Prenatal smoking might not cause attention-deficit/hyperactivity disorder: Evidence from a novel design	don't meet outcome criteria (maternal reported ADHD symptoms)
180.	Wilson et al.	2013	What predicts persistent early conduct problems? Evidence from the Growing Up in Scotland cohort	don't meet outcome criteria (maternal reported conduct disorder symptoms)
181.	Weitzman et al.	1992	Maternal smoking and behavior problems of children	don't meet outcome criteria (maternal reported ADHD symptoms)
182.	Wakschlag et al.	2006	Is prenatal smoking associated with a developmental pattern of conduct problems in young boys?	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
183.	Tiesler et al.	2011	Passive smoking and behavioural problems in children: results from the LISAplus prospective birth cohort study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
184.	Olson et al.	1997	Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence	don't meet outcome criteria (maternal reported conduct disorder symptoms)
185.	Alvik et al.	2013	Early fetal binge alcohol exposure predicts high behavioral symptom scores in 5.5-year-old children	don't meet outcome criteria (maternal reported conduct disorder, ADHD symptoms)
186.	Thapar et al.	2003	Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring	don't meet outcome criteria (maternal reported ADHD symptoms)

187.	Tanaka et al.	2016	Perinatal smoking exposure and behavioral problems in Japanese children aged 5 years: The Kyushu Okinawa Maternal and Child Health Study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
188.	Staroselsky et al.	2009	Both parental psychopathology and prenatal maternal alcohol dependency can predict the behavioral phenotype in children	don't meet outcome criteria (maternal reported conduct disorder symptoms)
189.	Piper and Corbett	2012	Executive function profile in the offspring of women that smoked during pregnancy	only unadjusted analyses
190.	Pfinder et al.	2012	Explanation of social inequalities in hyperactivity/inattention in children with prenatal alcohol exposure	don't meet outcome criteria (maternal reported ADHD symptoms)
191.	Romano et al.	2006	Development and prediction of hyperactive symptoms from 2 to 7 years in a population-based sample	don't meet outcome criteria (maternal reported ADHD symptoms)
192.	Ruckinger et al.	2010	Prenatal and postnatal tobacco exposure and behavioral problems in 10-year-old children: Results from the GINI-plus prospective birth cohort study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
193.	Ruisch et al.	2018	Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the Avon Longitudinal Study of Parents and Children	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
194.	Smidts and Oosterlaan	2007	How common are symptoms of ADHD in typically developing preschoolers? A study on prevalence rates and prenatal/demographic risk factors	don't meet outcome criteria (maternal reported ADHD symptoms)
195.	Van der Meer et al.	2017	Effects of dopaminergic genes, prenatal adversities, and their interaction on attention-deficit/hyperactivity disorder and neural correlates of response inhibition	don't meet outcome criteria (maternal reported ADHD symptoms)

196.	Motlagh et al.	2010	Severe psychosocial stress and heavy cigarette smoking during pregnancy: An examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome	only unadjusted analyses
197.	Monuteaux et al.	2006	Maternal smoking during pregnancy and offspring overt and covert conduct problems: A longitudinal study	don't meet outcome criteria (maternal reported conduct disorder symptoms)
198.	Miyake et al.	2018	Maternal caffeine intake in pregnancy is inversely related to childhood peer problems in Japan: The Kyushu Okinawa Maternal and Child Health Study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
199.	Milberger et al.	1997	Pregnancy, delivery and infancy complications and attention deficit hyperactivity disorder: Issues of gene-environment interaction	only unadjusted analyses
200.	Melchior et al.	2015	Maternal tobacco smoking in pregnancy and children's socio-emotional development at age 5: The EDEN mother-child birth cohort study	don't meet outcome criteria (maternal reported ADHD symptoms)
201.	McGee and Stanton	1994	Smoking in pregnancy and child development to age 9 years	don't meet outcome criteria (maternal reported ADHD symptoms)
202.	Maughan et al.	2001	Pregnancy smoking and childhood conduct problems: A causal association?	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
203.	Mattson et al.	2000	Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
204.	Loomans et al.	2012	Caffeine intake during pregnancy and risk of problem behavior in 5- to 6-year-old children	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)

205.	Lavigne et al.	2011	Is smoking during pregnancy a risk factor for psychopathology in young children? A methodological caveat and report on preschoolers	don't meet outcome criteria (maternal reported ADHD symptoms)
206.	Linnet et al.	2006	Cigarette smoking during pregnancy and hyperactive-distractible preschooler's: A follow-up study	don't meet outcome criteria (maternal reported ADHD symptoms)
207.	Kukla et al.	2008	Maternal smoking during pregnancy, behavioral problems and school performances of their school-aged children	don't meet outcome criteria (maternal reported measure ADHD symptoms)
208.	Kovess et al.	2015	Maternal smoking and offspring inattention and hyperactivity: results from a cross-national European survey	don't meet outcome criteria (maternal reported ADHD symptoms)
209.	Kotimaa et al.	2003	Maternal smoking and hyperactivity in 8-year-old children	don't meet outcome criteria (maternal reported ADHD symptoms)
210.	Knopik et al.	2016	Smoking during pregnancy and ADHD risk: A genetically informed, multiple-rater approach	don't meet outcome criteria (maternal reported ADHD symptoms)
211.	Knopik et al.	2009	Paternal alcoholism and offspring ADHD problems: A children of twins design	don't meet outcome criteria (maternal reported ADHD symptoms)
212.	Knopik et al.	2009	Genetic and environmental influences on externalizing behavior and alcohol problems in adolescence: a female twin study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
213.	Knopik et al.	2016	Within-family effects of smoking during pregnancy on ADHD: The importance of phenotype	duplicate
214.	Kieling et al.	2013	Gene-environment interaction in externalizing problems among adolescents: evidence from the Pelotas 1993 Birth Cohort Study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)

215.	Keyes et al.	2014	Associations of prenatal maternal smoking with offspring hyperactivity: Causal or confounded?	don't meet outcome criteria (maternal reported ADHD symptoms)
216.	Kendler et al.	2013	Dimensions of Parental Alcohol Use/Problems and Offspring Temperament, Externalizing Behaviors, and Alcohol Use/Problems	don't meet outcome criteria (maternal reported conduct disorder symptoms)
217.	Kelly et al.	2009	Light drinking in pregnancy, a risk for behavioural problems and cognitive deficits at 3 years of age?	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
218.	Kelly et al.	2012	Light drinking during pregnancy: Still no increased risk for socioemotional difficulties or cognitive deficits at 5 years of age?	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
219.	Kahn et al.	2003	Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors	don't meet outcome criteria (maternal reported ADHD symptoms)
220.	Jaspers et al.	2013	Early childhood assessments of community pediatric professionals predict autism spectrum and attention deficit hyperactivity problems	don't meet outcome criteria (maternal reported ADHD symptoms)
221.	Indredavik et al.	2007	Prenatal smoking exposure and psychiatric symptoms in adolescence	don't meet outcome criteria (maternal reported ADHD symptoms)
222.	Mikkelsen et al.	2017	Maternal Caffeine Consumption during Pregnancy and Behavioral Disorders in 11-Year-Old Offspring: A Danish National Birth Cohort Study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
223.	Hutchinson et al.	2010	Smoking in pregnancy and disruptive behaviour in 3-year-old boys and girls: An analysis of the UK millennium cohort study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)

224.	Huijbregts et al.	2007	Associations of maternal prenatal smoking with early childhood physical aggression, hyperactivity-impulsivity, and their co-occurrence	don't meet outcome criteria (maternal reported ADHD symptoms)
225.	Huijbregts et al.	2008	Hot and cool forms of inhibitory control and externalizing behavior in children of mothers who smoked during pregnancy: an exploratory study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
226.	Hannigan et al.	2010	A 14-year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
227.	Han et al.	2015	The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: A large population-based study	don't meet outcome criteria (maternal reported ADHD symptoms)
228.	Godel et al.	2000	Exposure to alcohol in utero: Influence on cognitive function and learning in a northern elementary school population	FAS sample
229.	Gilman et al.	2008	Maternal smoking during pregnancy and children's cognitive and physical development: A causal risk factor?	don't meet outcome criteria (observational data)
230.	Gatzke-Kopp and Beauchaine	2007	Direct and passive prenatal nicotine exposure and the development of externalizing psychopathology	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
231.	Fried et al.	1992	A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marijuana, cigarettes, and alcohol	don't meet outcome criteria (maternal reported ADHD symptoms)
232.	Fitzpatrick et al.	2014	Parental bad habits breed bad behaviors in youth: Exposure to gestational smoke and child impulsivity	don't meet outcome criteria (teacher reported ADHD symptoms)
233.	Fergusson et al.	1993	Maternal smoking before and after pregnancy: Effects on behavioral outcomes in middle childhood	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)

234.	Estabrook et al.	2016	Separating Family-Level and Direct Exposure Effects of Smoking During Pregnancy on Offspring Externalizing Symptoms: Bridging the Behavior Genetic and Behavior Teratologic Divide	don't meet outcome criteria (maternal reported conduct disorder, ODD and ADHD symptoms)
235.	Ellingson et al.	2014	A sibling-comparison study of smoking during pregnancy and childhood psychological traits	don't meet outcome criteria (maternal reported conduct disorder, ODD and ADHD symptoms)
236.	Eiden et al.	2018	Pre- and postnatal tobacco and cannabis exposure and child behavior problems: Bidirectional associations, joint effects, and sex differences	don't meet outcome criteria (maternal reported ADHD symptoms)
237.	Eichler et al.	2018	Effects of prenatal alcohol consumption on cognitive development and ADHD-related behaviour in primary-school age: a multilevel study based on meconium ethyl glucuronide	don't meet outcome criteria (maternal reported ADHD symptoms)
238.	Durr et al.	2015	Tobacco smoking during pregnancy and risk of adverse behaviour in offspring: A follow-up study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
239.	Dolan et al.	2016	Testing Causal Effects of Maternal Smoking During Pregnancy on Offspring's Externalizing and Internalizing Behavior	don't meet outcome criteria (maternal reported ADHD symptoms)
240.	Dodge et al.	2014	Protective effects of the alcohol dehydrogenase-ADH1B*3 allele on attention and behavior problems in adolescents exposed to alcohol during pregnancy	don't meet outcome criteria (teacher reported conduct disorder, ODD and ADHD symptoms)
241.	Disney et al.	2008	Strengthening the case: prenatal alcohol exposure is associated with increased risk for conduct disorder	don't meet outcome criteria (maternal reported conduct disorder symptoms)
242.	Desrosiers et al.	2013	Associations between prenatal cigarette smoke exposure and externalized behaviors at school age among Inuit children exposed to environmental contaminants	don't meet outcome criteria (teacher reported conduct disorder, ODD and ADHD symptoms)

243.	Sutin et al.	2017	Maternal cigarette smoking during pregnancy and the trajectory of externalizing and internalizing symptoms across childhood: Similarities and differences across parent, teacher, and self reports	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
244.	Sood et al.	2001	Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect	don't meet outcome criteria (maternal reported ADHD symptoms)
245.	Silberg et al.	2003	Maternal smoking during pregnancy and risk to boys' conduct disturbance: An examination of the causal hypothesis	don't meet outcome criteria (child's reported conduct disorder symptoms)
246.	Sen and Swaminathan	2007	Maternal prenatal substance use and behavior problems among children in the U.S	don't meet outcome criteria (maternal reported ADHD symptoms)
247.	Day et al.	2013	The association between prenatal alcohol exposure and behavior at 22 years of age	don't meet outcome criteria (maternal reported ADHD symptoms)
248.	Day et al.	2000	Effects of prenatal tobacco exposure on preschoolers' behavior	don't meet outcome criteria (maternal reported ODD and ADHD symptoms)
249.	D'Onofrio et al.	2008	Smoking during pregnancy and offspring externalizing problems: An exploration of genetic and environmental confounds	don't meet outcome criteria (maternal reported conduct disorder, ODD and ADHD symptoms)
250.	D'Onofrio et al.	2007	Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
251.	Cornelius et al.	2007	Smoking during teenage pregnancies: Effects on behavioral problems in offspring	don't meet outcome criteria (maternal reported ADHD symptoms)

252.	Cornelius et al.	2012	Long-term effects of prenatal cigarette smoke exposure on behavior dysregulation among 14-year-old offspring of teenage mothers	don't meet outcome criteria (maternal reported ADHD symptoms)
253.	Cornelius et al.	2012	Prenatal cigarette smoking: Long-term effects on young adult behavior problems and smoking behavior	externalising disorder not specified
254.	Cornelius et al.	2011	Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of adolescent mothers	don't meet outcome criteria (maternal reported ADHD symptoms)
255.	Clark et al.	2016	Developmental pathways from prenatal tobacco and stress exposure to behavioral disinhibition	don't meet outcome criteria (maternal reported ADHD symptoms)
256.	Chiu et al.	2009	Demographic and perinatal factors for behavioral problems among children aged 4-9 in Taiwan: Regular article	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
257.	Chiodo et al.	2010	The Impact of Maternal Age on the Effects of Prenatal Alcohol Exposure on Attention	don't meet outcome criteria (teacher reported ADHD symptoms)
258.	Carter et al.	2008	Maternal smoking during pregnancy and behaviour problems in a birth cohort of 2-year-old Pacific children in New Zealand	don't meet outcome criteria (maternal reported ADHD symptoms)
259.	Button et al.	2005	Relationship between antisocial behaviour, attention-deficit hyperactivity disorder and maternal prenatal smoking	don't meet outcome criteria (maternal reported ADHD symptoms)
260.	Buschgens et al.	2009	Externalizing behaviors in preadolescents: Familial risk to externalizing behaviors, prenatal and perinatal risks, and their interactions	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
261.	Brown et al.	1991	Effects of prenatal alcohol exposure at school age. II. Attention and behavior	don't meet outcome criteria (maternal and teacher reported conduct disorder and ADHD symptoms)

262.	Brion et al.	2010	Maternal smoking and child psychological problems: Disentangling causal and noncausal effects	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
263.	Brinksma et al.	2017	Age-dependent role of pre- and perinatal factors in interaction with genes on ADHD symptoms across adolescence	don't meet outcome criteria (maternal reported ADHD symptoms)
264.	Brennan et al.	2011	Interactions between the COMT Val108/158Met polymorphism and maternal prenatal smoking predict aggressive behavior outcomes	don't meet outcome criteria (child's, maternal and teacher reported ADHD symptoms)
265.	Bos-Veneman et al.	2010	Role of perinatal adversities on tic severity and symptoms of attention deficit/hyperactivity disorder in children and adolescents with a tic disorder	don't meet outcome criteria (maternal reported ADHD symptoms)
266.	Boden et al.	2010	Risk factors for conduct disorder and oppositional/defiant disorder: Evidence from a New Zealand birth cohort	don't meet outcome criteria (maternal reported ODD and ADHD symptoms)
267.	Bekkhus et al.	2010	Intrauterine exposure to caffeine and inattention/overactivity in children	don't meet outcome criteria (maternal reported ADHD symptoms)
268.	Becker et al.	2008	Interaction of Dopamine Transporter Genotype with Prenatal Smoke Exposure on ADHD Symptoms	don't meet outcome criteria (maternal reported ADHD symptoms)
269.	Batstra et al.	2003	Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in childhood: Prospective evidence from a Dutch birth cohort	don't meet outcome criteria (maternal reported ADHD symptoms)
270.	Arruda et al.	2015	ADHD and mental health status in Brazilian school-age children	only unadjusted analyses
271.	Anselmi et al.	2010	Early determinants of attention and hyperactivity problems in adolescents: the 11-year follow-up of the 1993 Pelotas (Brazil) birth cohort study	externalising disorder not specified

272.	Agrawal et al.	2010	The effects of maternal smoking during pregnancy on offspring outcomes	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
273.	Sayal et al.	2007	Prenatal alcohol exposure and gender differences in childhood mental health problems: A longitudinal population-based study	don't meet outcome criteria (maternal and teacher reported conduct disorder and ADHD symptoms)
274.	Sayal et al.	2009	Binge pattern of alcohol consumption during pregnancy and childhood mental health outcomes: longitudinal population-based study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
275.	Sayal et al.	2014	Prenatal exposure to binge pattern of alcohol consumption: mental health and learning outcomes at age 11	don't meet outcome criteria (maternal and teacher reported conduct disorder and ADHD symptoms)
276.	Salationo-Oliveira et al.	2016	COMT and prenatal maternal smoking in associations with conduct problems and crime: the Pelotas 1993 birth cohort study	don't meet outcome criteria (maternal reported conduct disorder symptoms)
277.	Rodriguez et al.	2009	Is prenatal alcohol exposure related to inattention and hyperactivity symptoms in children? Disentangling the effects of social adversity	don't meet outcome criteria (maternal and teacher reported ADHD symptoms)
278.	Rodriguez and Bohlin	2005	Are maternal smoking and stress during pregnancy related to ADHD symptoms in children?	don't meet outcome criteria (maternal reported ADHD symptoms)
279.	Pourcain et al.	2011	Links between co-occurring social-communication and hyperactive-inattentive trait trajectories	don't meet outcome criteria (maternal reported ADHD symptoms)

280.	Piper et al.	2012	Maternal smoking cessation and reduced academic and behavioral problems in offspring	don't meet outcome criteria (maternal reported ADHD symptoms)
281.	Pfinder et al.	2014	Impact of moderate prenatal alcohol exposure on problem behaviors in preschool and school children stronger effects in disadvantaged populations? Results from the KiGGS study	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
282.	Parker et al.	2016	Prenatal smoking and childhood behavior problems: is the association mediated by birth weight?	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
283.	Park et al.	2014	Mediating role of stress reactivity in the effects of prenatal tobacco exposure on childhood mental health outcomes	don't meet outcome criteria (maternal and teacher reported conduct disorder and ADHD symptoms)
284.	Palmer et al.	2016	Effects of Maternal Smoking during Pregnancy on Offspring Externalizing Problems: Contextual Effects in a Sample of Female Twins	don't meet outcome criteria (child's and maternal reported conduct disorder and ADHD symptoms)
285.	Palili et al.	2011	Inattention, hyperactivity, impulsivity--epidemiology and correlations: a nationwide greek study from birth to 18 years	don't meet outcome criteria (maternal reported ADHD symptoms)
286.	Orlebeke et al.	1999	Child behavior problems increased by maternal smoking during pregnancy	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
287.	Orlebeke et al.	1997	Increase in child behavior problems resulting from maternal smoking during pregnancy	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)

288.	Obel et al.	2009	Smoking during pregnancy and hyperactivity-inattention in the offspring - Comparing results from three Nordic cohorts	don't meet outcome criteria (maternal reported ADHD symptoms)
289.	O'Leary et al.	2010	Evidence of a complex association between dose, pattern and timing of prenatal alcohol exposure and child behaviour problems	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
290.	Noordermeer et al.	2017	Risk factors for comorbid oppositional defiant disorder in attention-deficit/hyperactivity disorder	no exposure-outcome association measured
291.	Niclasen et al.	2014	Prenatal exposure to alcohol, and gender differences on child mental health at age seven year	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
292.	Niclasen et al.	2014	Is alcohol binge drinking in early and late pregnancy associated with behavioural and emotional development at age 7 years?	don't meet outcome criteria (maternal reported conduct disorder and ADHD symptoms)
293.	Murray et al.	2010	Very early predictors of conduct problems and crime: results from a national cohort study	don't meet outcome criteria (maternal reported conduct disorder symptoms)
294.	Murray et al.	2016	Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: causal effects in a Mendelian randomisation study	don't meet outcome criteria (maternal reported conduct disorder symptoms)
295.	Hill et al.	2000	Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders" - did not any adjusted results on tobacco and alcohol exposure and ADHD, CD and ODD	results not reported

Appendix 2.6. List of studies not reporting all the results

Author/Year	Title	Country	Study design	Exposure	Outcome	Missing data
Talati et al., 2016	Brain derived neurotrophic factor moderates associations between maternal smoking during pregnancy and offspring behavioral disorders"	USA	Longitudinal family study	Smoking	ADHD CD	Results not reported on ADHD due to the low number of cases
Talati et al., 2017	Prenatal tobacco exposure, birthweight, and offspring psychopathology" – did not report ADHD results due to the low number of cases	USA	Longitudinal family study	Smoking	ADHD CD	Results not reported on ADHD due to the low number of cases
Whitbeck et al., 2009	Gestational risks and psychiatric disorders among indigenous adolescents" – did not report results on tobacco exposure and ADHD	USA	Cohort study	Smoking Alcohol	ADHD CD	Results on smoking exposure not reported
Hill et al., 2000	Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders" – did not any adjusted results on tobacco and alcohol exposure and ADHD, CD and ODD	USA	Longitudinal family study	Smoking Alcohol	ADHD CD ODD	Adjusted results not reported
Kim et al., 2009	Perinatal and Familial Risk Factors Are Associated with Full Syndrome and Subthreshold Attention-Deficit Hyperactivity Disorder in a Korean Community Sample	Korea	Case-control	Smoking Alcohol Caffeine	ADHD	Results not reported on smoking exposure due to the low prevalence of smoking in the sample
Knopik et al., 2006	Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design	Australia	Longitudinal twin study	Smoking Alcohol	ADHD	Only unadjusted results reported for alcohol exposure

Appendix 2.7. Study characteristics and results of cohort, longitudinal and cross-sectional studies

Author/Year	Country	Study sample	Cases/total sample size	Gender	Offspring age at assessment	Exposure assessment	Classification of exposure	Outcome	Outcome assessment	Follow up time	Confounders	Results (as reported in the study)
Smoking												
Ball et al., 2010	USA	Prospective longitudinal cohort study in general population (the Collaborative Perinatal Project (CPP), the new England Family Study (NEFS) and Providence cohort	219/2024	Both	37.2 years	Prospective self-report during all the pregnancy trimesters	No smoking (ref); <half pack per day; >half pack to <full pack; <full pack	ADHD	Retrospective assessment using Diagnostic interview Schedule (DIS)	1, 4, 7 years and adulthood	Ascertainment source, family psychopathology, maternal education, offspring gender	**OR (95% CI)** No smoking (ref) <half pack per day: 1.2 (0.81, 1.7) >half pack to <full pack: 1.1 (0.75, 1.6) >full pack: 1.1 (0.67, 1.8)
Gustavson et al., 2017	Norway	Prospective longitudinal birth cohort study in general population (the Norwegian Mother, Father and Child Cohort study (MoBa))	2035/104,846	Both	5 years	Prospective self-report during the 2nd and 3rd pregnancy trimester	Binary (Yes/No)	ADHD	ADHD diagnosis obtained from the Norwegian Patient Registry (NPR)	6, 18 months, 3, 5, 7, 8 and 13 years (ongoing study)	Parental age, education, parental ADHD symptoms; maternal (pre-pregnancy) and paternal BMI; maternal alcohol consumption during pregnancy; maternal parity; child's birth year; geographical residential region	**Hazard ratio (HR) (95% CI), p-value** 1.48 (1.3, 1.68), <0.001 **the magnitude of the effect size was similar in all negative controls (paternal smoking, grandmother's smoking when pregnant with the mother, and maternal smoking in previous pregnancies)*
Langley et al., 2012	UK	Prospective longitudinal birth cohort study in general population (the Avon Longitudinal Study of Parents and Children (ALSPAC))	121/5637	Both	7.6 years	Prospective self-report during the 2nd and 3rd pregnancy trimester	No smoking (ref); 1-9 cigarettes/day; 10-19 cigarettes/day; >20 cigarettes/day	ADHD	the Development and Well-Being Assessment (DAWBA) and diagnosis were generated based on maternal and teacher reports	From birth to adulthood (ongoing study)	child's sex, ethnicity, multiple births (twins), maternal prenatal alcohol use, social class	**OR (95% CI), p-value** 1.72 (1.14, 2.61), <0.05 **the magnitude of the effect estimates were similar with paternal smoking*
Obel et al., 2011	Finland	Population based cohort and registry study	7023/868,449 6013 boys 1010 girls	Both (reported separately for boys and girls)	15 years	Information collected during the routine visit to midwives in the 1st and 2nd pregnancy trimester	Non-smokers (ref); Smokers Non-smokers (ref); 1-9 cigarettes/day; 10+ cigarettes/day; Non-smokers (ref); Only 1st trimester; After first trimester	Hyperkinetic disorder	the Finnish Hospital Discharge Register (FHDR)	15 years	child age, birth year, child sex, gestational age at birth, parity, maternal age, SES	**HR (95% CI), p-value** Total sample: 2.01 (1.9, 2.12) Boys: 1.96 (1.85, 2.08) Girls: 2.28 (1.99, 2.63) <u>Total sample:</u> Overall: 1.92 (1.69, 2.18) 1-9 cigarettes: 1.77 (1.47, 2.12) 10+ cigarettes: 2.03 (1.74, 2.37) <u>Boys:</u> Overall: 1.88 (1.64, 2.15) 1-9 cigarettes: 1.75 (1.43, 2.13) 10+ cigarettes:

												1.97 (1.67, 2.33) Girls: Overall: 2.23 (1.56, 3.18) 1-9 cigarettes: 1.93 (1.15, 3.23) 10+ cigarettes: 2.46 (1.59, 3.81) Total sample: Overall: 1.92 (1.80, 2.04) Only 1st trimester: 1.34 (1.11, 1.62) After 1st trimester: 1.98 (1.86, 2.12) Boys: Overall: 1.88 (1.75, 2.01) Only 1st trimester: 1.34 (1.09, 1.64) After 1st trimester: 1.94 (1.81, 2.08) Girls: Overall: 2.13 (1.82, 2.49) Only 1st trimester: 1.35 (0.82, 2.22) After 1st trimester: 2.21 (1.88, 2.60) **no difference in effect estimates in sibling comparison analyses*
Obel et al., 2016	Denmark	Population based cohort and registry study	17,381/968,665 13,524 boys 3857 girls	Both (reported separately for boys and girls)	9 years	Information collected during the visits to general practitioners in each pregnancy trimester	Non-smokers (ref); Smokers Non-smokers (ref); Quitted smoking during 1st trimester; Continued smoking Non-smokers (ref); 1-10cigarettes/day; 10+ cigarettes	Hyperkinetic disorder	ADHD diagnosis obtained from the ICD-10 registration system and ADHD medication obtained from the Register of Medicinal Product Statistics	Median follow up time 9 years	birth year, child sex, maternal age, and parity	**HR (95% CI)** Total sample : 2.01 (1.94, 2.07) Boys : 1.98 (1.91, 2.05) Girls: 2.12 (1.99, 2.27) No smoking (ref) Quitted smoking during 1st trimester: 1.61 (1.39, 1.88) Continued smoking: 2.19 (2.09, 2.29) No smoking (ref) 1-10 cigarettes: 1.92 (1.81, 2.02) 10+ cigarettes: 2.77 (2.60, 2.95) **no associations in sibling analyses"*
Skoglund et al., 2014	Sweden	Population based registry study	19,891/768,227	Both	~9 years	Antenatal visit during the 1st pregnancy trimester	No smoking (ref); Moderate (1-9 cigarettes); High (>10 cigarettes)	ADHD	Diagnosis and medication use of ADHD were identified from the Patient	Up to 9 years	child sex, birth year, parity, maternal age at child's birth, cohabitation with the child's father, maternal education, mother's country of birth	**HR (95% CI)** Moderate: 1.62 (1.56, 1.69) High: 2.04 (1.95, 2.13)

									Register and the Swedish Prescribed Drug register			*no association in sibling and cousin analyses
Zhu et al., 2014	Denmark	Population based longitudinal and registry study (Danish Birth Cohort Study)	2009/84,803	Both	>5 years	Interview during the 2nd pregnancy trimester	Non-smoker (ref); Smoker; Nicotine replacement user; Smoking quitter	ADHD	A combination of ADHD medication and hospital diagnosis (the International Classification of Diseases, 10th Revision [ICD-10]) was used.	Up to 8 to 14 years	maternal age at birth of the child, alcohol intake during pregnancy, parental socio-occupational status, parental psychopathology, parity and child's gender	**HR (95% CI)** Smoking (both parents): 1.83 (1.60, 2.10) Smoking (father non-smoker): 1.63 (1.36, 1.94) *stronger association with maternal smoking and nicotine replacement when father was non-smoker*
Lindblad et al., 2010	Sweden	Population based registry study	6141/927,007	Both	6-19 years	Visit to the midwives during the 1st pregnancy trimester	No smoking in any pregnancy (ref); No smoking at least in one pregnancy; 1-9 cigarettes/day; 10+ cigarettes/day	ADHD	ADHD medication use was obtained from The Swedish Prescribed Drug Register	from 6 up to 19 years	maternal age and year of birth, child sex, and parity. Marital status, maternal education, social assistance, parental psychiatric disorders and substance use, child's indicator of small for gestational age (gestational age and Apgar score)	**OR (95% CI)** No smoking at least in one pregnancy: 1.43 (1.26, 1.61) 1-9 cigarettes: 1.59 (1.49, 1.70) 10+ cigarettes: 1.89 (1.75, 2.04) *no association within-mother between pregnancy analyses*
Braun et al.., 2006	USA	population based cross-sectional study (The National Health and Nutrition Examination Survey (NHANES))	135/4704	Both (reported separately for boys and girls)	4-15 years	Not specified	Binary (Yes/No)	ADHD	Combination of parent report whether child has diagnosed for ADHD and stimulant medication use based on National Drug Codes	NA	child's age, sex, race, socioeconomic status as measured by poverty-to-income ratio (PIR), mother's age at child's birth, national insurance coverage, preschool attendance and perinatal distress (birth weight and admission to neonatal intensive care unit)	**OR (95% CI), p-value** Total sample: 2.5 (1.2, 5.2), 0.02 Boys: 2.1 (0.9, 4.7), 0.07 Girls: 4.6 (1.7, 12.4)
Wakschlag et al., 1997	USA	longitudinal study (clinic referred sample)	105/177	only boys	12-17 years	retrospective self-report (pregnancy trimester not specified)	No and occasional smoking (ref); Smoked <half pack/day; Smoked >half pack/day	CD	A diagnosis was derived by combining parent, teacher and child report of the National Institute of Mental Health Diagnostic Interview Schedule for Children (DISC)	4 annual assessments (starting age 7 years) and 5th assessment in 2 years	SES and ethnicity, parental psychopathologic conditions (paternal antisocial personality disorder, maternal MMPI antisocial index, and maternal and paternal depression and substance abuse), other pregnancy risk factors (maternal age at child's birth, use of illicit drugs and alcohol during pregnancy, pregnancy and birth complications, low birth weight, and prematurity), and family and parenting risk factors (number of children in the household, marital status, poor communication, little supervision, and ineffective and harsh discipline	**OR (95% CI), p-value** Smoked <half pack/day: 1.6 (0.53, 5.11), 0.39 Smoked >half pack/day: 3.3 (1.2, 9.07), 0.02
Talati et al., 2016	USA	longitudinal family study (clinical sample	- /209	both	not specified	retrospective self-report (pregnancy	Binary (smoked >10 cigarettes/did not	CD	Semi-structured interview (Schedule for Affective	Six waves up to 30 years	age, gender, and maternal depression and substance use history	Effect estimate (SE), p-value Smoking: 0.15 (0.51), 0.76

		of depressed probands)				trimester not specified)	smoke >10 cigarettes/day)		Disorders and Schizophrenia, SADS) administered by trained mental health professional			Smoking and child genotype interaction: 1.92 (0.81), 0.017
Braun et al., 2008	USA	population based cross-sectional study (The National Health and Nutrition Examination Survey (NHANES))	68/3081	both	8-15 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	CD	the Diagnostic Interview Schedule for Children (DISC) based on DSM-IV criteria	NA	child's age, sex, race, socioeconomic status as measured by poverty-to-income ratio (PIR), and mother's age at child's birth	**OR (95% CI)** 3.00 (1.36, 6.63)
Ellis et al., 2012	Norway	population based prospective cohort study (the Trondheim Early Secure Study (TESS))	995 34 ADHD cases 57 ODD cases	both	4 years	retrospective interview (assessed in each pregnancy trimester)	Binary (Yes/No)	ADHD ODD	Structured interview with mothers using the Preschool Age Psychiatric Assessment (PAPA – diagnosis based on DSM-IV criteria)	4 years (ongoing)	Personality traits of narcissistic, histrionic, borderline, schizotypal, paranoid, avoidant, dependent, obsessive-compulsive personality, parental alcohol use, parental anxiety, depression, prenatal stress, depression, alcohol use, planned pregnancy, parental feelings about pregnancy, mothers' feelings in the first month after birth, parental experience of mental breakdown, parent requested medical treatment, parent ever been arrested, parent ever been indicted by police, parental ability to pay family expenses, parent received medical treatment for psychological disorder, and parental admission to a mental health institution. Maternal age and SES	**OR (95% CI), p-value** ADHD: 2.17 (1.3, 3.61), 0.003 ODD: 2.46 (1.66, 3.63), 0.001 **propensity score analyses*
Nigg et al., 2007	USA	longitudinal cohort study	798 95 ADHD cases 46 CD cases 89 ODD cases	both	11 years in ADHD 17 years in CD and ODD	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD CD ODD	the Diagnostic Interview Schedule for Children (DISC; version 2.1)	3 assessments: at age 6, 11 and 17 years	low birth weight, maternal substance use disorders, maternal education, home environment (urban vs suburban)	**OR (95% CI), p-value** ADHD: 1.19 (0.79, 1.8) CD: 2.32 (1.05, 5.15), <0.05 ODD: 2.31 (1.24, 4.31), <0.05 **low birth weight did not mediate the association with ADHD. Independent effect of low birth weight was observed on ADHD but not on CD or ODD*
Talati et al., 2017	USA	longitudinal family study (clinical sample of depressed mothers)	238 21 ADHD cases 66 CD cases	Both (reported separately for boys and girls)	6-17 years	retrospective self-report (pregnancy trimester not specified)	Binary (whether or not mother smoked >10 cigarettes/day)	CD	Semi-structured interview (Schedule for Affective Disorders and Schizophrenia, SADS) administered by trained mental health professional	6 waves (age 1, 2, 10, 20 and 30 years). Mean follow-up time 27.7 years	Familial risk for depression, offspring age at final interview, and sex (except in the sex-specific models). Further covariates included lifetime diagnosis of nicotine dependence in either parent and any parental mental health diagnosis	**OR (95% CI), p-value** Total sample: 1.75 (0.94, 3.23), <0.07 Boys: 2.63 (1.05, 6.49), <0.05 Girls: 1.08 (0.41, 2.82) **birth weight did not mediate the association*

Weissman et al., 1999	USA	longitudinal family study (clinical sample of depressed mothers)	-/147	Both (reported separately for boys and girls)	16.4 years	retrospective self-report (pregnancy trimester not specified)	Binary (no smoking; 10+ cigarettes/day)	CD ADHD	Parent and offspring interview using the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-LA)	3 assessments in 10 years: baseline 6 to 23 years	history of maternal depression, offspring age and divorce	**Relative Risk (RR) (95% CI)** CD 13-17 years: Boys: 1.70 (0.48, 5.96) Girls: 1.00 (0.35, 2.86) ADHD <13 years: Boys: 0.44 (0.09, 2.09) Girls: 2.16 (0.14, 34.71)
Nomura et al., 2010	USA	longitudinal study	209 65 ADHD cases 6 ODD cases	both	4.3 years	retrospective self-report	Binary (Yes/No)	ADHD ODD	Semi-structured child psychiatric interview (the Kiddie-SADS-PL) administered to a parent	baseline age 3-4 years	Child's age, gender, SES, birth weight, and ethnicity, self-report of maternal and paternal ADHD symptoms, and maternal alcohol use during pregnancy	**OR (95% CI), p-value** ADHD: 4 (1.36, 11.12), 0.012 ODD: 3.37 (0.22, 38.46), 0.34 **stronger association with maternal smoking compared to paternal smoking in ADHD*
Fergusson et al., 1998	New Zealand	prospective longitudinal cohort study (the Christchurch Health and Development Study)	-/1022	both	16-18 years	Prospective self-report during each pregnancy trimesters	No smoking; 1-9 cigarettes/day; 10-19 cigarettes/day; 20+ cigarettes/day	CD	the Composite International Diagnostic Interview and the Self-Report Delinquency Inventory. DSM-IV criteria were used for constructing diagnosis	At birth, 4 months, annual assessment up to 16 years and 18 years	Maternal education, age, family SES, pregnancy planning, prenatal alcohol and illicit drug use, maternal child-rearing practices, parental separation, parental conflict, parental history of alcohol problems, criminal offending and illicit drug use	**OR (95% CI), SE, p-value** 1.27 (0.9, 1.78), 0.17, 0.172 **exposure treated in continuous scale*
Koshy et al., 2011	UK	cross-sectional study (preselected areas of lower socio-economic status)	29/1074	both	7.3 years	retrospective self-report (pregnancy trimester not specified)	No smoking (ref); Light: <10 cigarettes/day; Heavy: >10 cigarettes/day	ADHD	Parent report whether child has been diagnosed for ADHD by a doctor	NA	child obesity and overweight, doctor-diagnosed asthma, preterm birth, household member smoking during pregnancy, low birthweight	**OR (95% CI), p-value** Total smoking: 2.20 (1.08, 9.49), 0.04 Light: 2.89 (0.38, 22.09) Heavy: 10.03 (1.62, 61.99), 0.013
Pohlabeln et al., 2017	Multiple countries (Belgium, Cyprus, Estonia, Hungary, Italy, Spain, Sweden)	prospective cohort study in general population (the European IDEFICS study – Identification and prevention of dietary- and lifestyle-induced health effects in children and infants)	152/15,277	both	6.2 years	retrospective self-report (pregnancy trimester not specified)	Never (ref); <1 a month; Several occasions a week/daily	ADHD	Maternal report – "Has the child ever been diagnosed for ADHD?	2 years (baseline age range 2-11.9 years)	child's sex, age, country, maternal age, SES and further for gestational hypertension, proteinuria, sugar in urine (glycosuria), and gestational diabetes, weight and height of the child at birth, potential health problems (respiratory adjustment disorders or infections), the duration of breastfeeding (exclusive and in combination with other types of feeding), and, in case of preterm birth, the number of weeks the child was born before the estimated date of birth.	**OR (95% CI), p-value** Several occasions week/daily: 1.74 (1.13, 2.67), 0.02 **adjusted results reported only for heavier smoking*
Sagiv et al., 2013	USA	prospective cohort study in general population (the New Bedford Cohort study)	75/604	both	8 years	retrospective self-report (pregnancy trimester not specified)	No smoking (ref); 1-10 cigarettes/day >10 cigarettes/day	ADHD	Diagnosis were obtained from the paediatric medical records and parents were asked to report whether the child	8 years	maternal age at offspring birth and education, paternal education, annual household income, marital status, prenatal substance use, maternal IQ, maternal depression (postnatal), HOME score, child age, gestational	**RR (risk ratio) (95% CI), p-value** 1-10 cigarettes: 0.9 (0.4, 1.8), 0.68 >10 cigarettes: 1.6 (0.8, 3.2), 0.20

									was regularly taking ADHD medications		age, sex, ethnicity, breast feeding, school type, number of siblings	
Schmitt et al., 2012	Germany	cross-sectional study in general population (the German Health Interview and Examination Survey for Children and Adolescents (KIGGS)	660/13,488	both	9.9 years	not specified	Binary (Yes/No)	ADHD	lifetime diagnosis of ADHD on the basis of medical or psychological examination as reported in standardized parental interviews conducted by trained interviewers	NA	child gender, age, SES (based on parental education, professional qualification, family income), maternal gestational diabetes, perinatal health problems, breastfeeding, atopic eczema	**OR (95% CI)** 1.48 (1.19, 1.84)
Sciberras et al., 2011	Australia	population-based longitudinal study (the Longitudinal Study of Australian Children (LSAC)	64/3781	both	6.8 years	retrospective self-report (pregnancy trimester not specified)	No smoking (ref); Occasionally; Most days	ADHD	Primary caregiver report – "Does the study child have ADHD?"	2 years (baseline age 4-5 years)	maternal age, education, marital status, number of people in the household, child gender, household income, child's birth weight, maternal postnatal depression, intensive care at birth	**OR (95% CI), p-value** Occasionally: 0.62 (0.17, 2.26) Most days: 3.31 (1.49, 7.39), 0.004
Lehn et al., 2007	the Netherlands	longitudinal twin study (the Netherlands Twin Registry)	34/190	both	13.4 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Clinical Interview (DISC-IV Parent Version)	assessment at age 1, 2, 3, 5, 7, 10 and 12 years	Discordant and concordant pairs were matched on gender, zygosity, date of birth, maternal age, and parental SES. In wave II matching criteria was gender, date of birth, zygosity, handedness, and SES	**prenatal maternal smoking was more common in MZ pairs concordant for Aps/ADHD than in the other groups, providing at least secondary evidence that smoking, in addition to a common genetic risk, leads to increased rates of ADHD in offspring*
Russell et al., 2015	USA	cross-sectional study (household survey in general population)	-/5924	both (reported separately for boys and girls)	15.3 years	retrospective self-report (pregnancy trimester not specified)	More than 20 cigarettes per day; 11 to 20 cigarettes per day; 1 to 10 cigarettes per day; Fewer than 1 cigarette per day; None (ref)	ODD	Structured diagnostic interview (CIDI – The World Health Organization's Composite International Diagnostic Interview)	NA	offspring age	**OR (95% CI)** Total sample: 1.06 (0.8, 1.3) Boys: 1.00 (0.7, 1.4) Girls: 1.11 (0.8, 1.5)
Froehlich et al., 2009	USA	Cross-sectional study (household survey in general population)	215/2588	both	8-15 years	Retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Diagnostic Interview Schedule for Children (DISC)	NA	child age, ethnicity and gender, household income/poverty ratio, mother's age at child's birth, birth weight, NICU admission, postnatal secondhand smoke exposure, preschool attendance, health insurance status	**OR (95% CI), p-value** 2.4 (1.5, 3.7), 0.001
Knopik et al., 2005	USA	Longitudinal twin study (the Missouri Adolescent Female Twin Study)	128/1936	girls	14.4 years	Retrospective interview (assessed 1st trimester and beyond 1st trimester)	First trimester: 1-10 cigarettes/day; 11-19 cigarettes/day; >20 cigarettes/day Beyond first trimester:	ADHD	the Diagnostic Interview for Children and Adolescents (DICA)	recruitment over 2 years – 13, 15, 17 and 19 years	zygosity, prenatal and parental predictors – low birth weight, maternal alcohol abuse/dependence, paternal alcohol dependence, frequent heavy drinking during pregnancy	**OR (95%CI)** First trimester: 0.97 (0.5, 1.86) 1-10 cigarettes/day: 1.05 (0.48, 2.37) 11-19 cigarettes/day: 0.42 (0.11, 1.63) >20 cigarettes/day:

							1-10 cigarettes/day; 11-19 cigarettes/day; >20 cigarettes/day					1.40 (0.48, 4.07) Beyond first trimester: 1.50 (0.86, 2.63) 1-10 cigarettes/day: 1.24 (0.61, 2.52) 11-19 cigarettes/day: 1.83 (0.89, 3.76) >20 cigarettes/day: 1.79 (0.79, 4.07)
Knopik et al., 2006	Australia	Longitudinal twin study	-/922	both	13-21 years	Retrospective interview (assessed 1st trimester and beyond 1st trimester)	Never smoked; Regular smoker, not during pregnancy; 1st trimester only Beyond 1st trimester, 1–15 cigarettes/day; Beyond 1st trimester, 16+ cigarettes/day	ADHD	the Diagnostic Interview for Children and Adolescents (DICA)	Not specified	child gender and age, paternal history of alcohol problems and paternal conduct disorder/antisociality history	**OR (95% CI), p-value** Never smoked (ref) Regular smoker, not during pregnancy: 0.72 (0.23, 2.22) 1st trimester only: 1.88 (0.45, 7.81) Beyond 1st trimester, 1–15 cigarettes/day: 0.54 (0.16, 1.83) Beyond 1st trimester, 16+ cigarettes/day: 3.83 (1.09, 13.45), <0.005
Alcohol												
Fergusson et al., 1998	New Zealand	prospective longitudinal cohort study (the Christchurch Health and Development Study)	-/1022	both	16-18 years	Prospective self-report during each pregnancy trimester	No drinking (ref); 1-3 drinks/week; 4-6 drinks/week; 7+ drinks/week	CD	the Composite International Diagnostic Interview and the Self-Report Delinquency Inventory. DSM-IV criteria were used for constructing diagnosis	At birth, 4 months, annual assessment up to 16 years and 18 years	Maternal education, age, family SES, pregnancy planning, prenatal smoking and illicit drug use, maternal child-rearing practices, parental separation, parental conflict, parental history of alcohol problems, criminal offending and illicit drug use	**OR (95% CI), SE, p-value** 1.32 (0.93, 1.88), 0.18, 0.126 **exposure treated in continuous scale*
Larkby et al., 2011	USA	longitudinal birth cohort study	67/487	both	16.8 years	Prospective self-report in each pregnancy trimester (focus on 1st and 3rd pregnancy trimester)	Alcohol consumption based on average daily volume (ADV) No drinking (ref); Light (ADV <0.4); Moderate (0.4-0.89); Heavy (>0.89)	CD	the Diagnostic Interview Schedule-IV (DIS-IV).	At delivery, 8 and 18 months, 3, 6, 10, 14, 16 and 22 years	prenatal exposure to marijuana, cocaine, and other illicit drugs, income, child's race, age and gender, parenting style, life events, home environment, family history of alcohol problems, and maternal lifetime psychopathology	**OR (95% CI)** First trimester: Heavy: 2.47 (1.3, 4.7) **Results not reported for other categories and drinking in the 3rd trimester*
Pohlabeln et al., 2017	Multiple countries (Belgium, Cyprus, Estonia, Hungary, Italy, Spain, Sweden)	prospective cohort study in general population (the European IDEFICS study – Identification and prevention of dietary- and lifestyle-induced health effects in children and infants)	152/15,277	both	6.2 years	retrospective self-report (pregnancy trimester not specified)	Never (ref); <1 a month; Several occasions a month/week	ADHD	Maternal report – "Has the child ever been diagnosed for ADHD?"	2 years (baseline age range 2-11.9 years)	child's sex, age, country, maternal age, SES and further for gestational hypertension, proteinuria, sugar in urine (glycosuria), and gestational diabetes, weight and height of the child at birth, potential health problems (respiratory adjustment disorders or infections), the duration of breastfeeding (exclusive and in combination with other types of feeding), and, in case of preterm birth,	**OR (95% CI), p-value** Several occasions month/week: 0.76 (0.23, 2.48), 0.65 **adjusted results reported only for heavier drinking*

											the number of weeks the child was born before the estimated date of birth.	
Sagiv et al., 2013	USA	prospective cohort study in general population (the New Bedford Cohort study)	75/604	both	8 years	prospective self-report 2 weeks after child's birth (pregnancy trimester not specified)	<1 serving/month (ref); 1-2 servings/month >2 servings/month	ADHD	Diagnosis were obtained from the paediatric medical records and parents were asked to report whether the child was regularly taking ADHD medications	8 years	maternal age at offspring birth and education, paternal education, annual household income, marital status, prenatal substance use, maternal IQ, maternal depression (postnatal), HOME score, child age, gestational age, sex, ethnicity, breast feeding, school type, number of siblings	**RR (95% CI), p-value** 1-2 servings: 2.5 (0.8, 7.2), 0.1 >2 servings: 0.8 (0.3, 2.1), 0.71
Schmitt et al., 2012	Germany	cross-sectional study in general population (the German Health Interview and Examination Survey for Children and Adolescents (KIGGS)	660/13,488	both	9.9 years	not specified	Binary (Yes/No)	ADHD	lifetime diagnosis of ADHD on the basis of medical or psychological examination as reported in standardized parental interviews conducted by trained interviewers	NA	child gender, age, SES (based on parental education, professional qualification, family income), maternal gestational diabetes, perinatal health problems, breastfeeding, atopic eczema	**OR (95% CI)** 1.02 (0.79, 1.33)
Whitbeck et al., 2009	USA	cohort study (lagged sequential) (population based on indigenous culture)	-/546	both	10-15 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	CD	diagnostic interview (the Diagnostic Interview Schedule for Children-Revised (DISC-R) with parents and children	4 annual assessments (baseline age 10-12 years)	child age, gender, marital status, income, parenting behaviour (maternal warmth, support and maternal approval)	**OR, p-value** Binge drinking: 3.29, <0.01
Russell et al., 2015	USA	cross-sectional study (household survey in general population)	-/5924	both (reported separately for boys and girls)	15.3 years	retrospective self-report (pregnancy trimester not specified)	Everyday; 3 to 5 times per week; 1 to 2 times per week; 1 to 3 times per month; Less than once per month; Never (ref)	ODD	Structured diagnostic interview (CIDI – The World Health Organization's Composite International Diagnostic Interview)	NA	child age	**OR (95% CI)** Total sample: 0.56 (0.3, 1.1) Boys: 0.56 (0.2, 1.5) Girls: 0.52 (0.2, 1.5)
Eilertsen et al., 2017	Norway	prospective longitudinal birth cohort study (MoBa)	220/34,283	both	5 years	prospective self-report (assessed during the 1st pregnancy trimester)	continuous score of AUDIT scale	ADHD	Diagnosis of hyperkinetic disorder obtained from the National Patient Registry	6, 18 months, 3, 5, 7, 8 and 13 years (ongoing study)	parental education and income, maternal smoking during pregnancy, children's birth order and children's gender	**OR (95% CI)** 0.97 (0.93, 1.01)
Knopik et al., 2005	USA	Longitudinal twin study (the Missouri Adolescent Female Twin Study)	128/1936	girls	14.4 years	Retrospective interview (assessed 1st trimester and beyond 1st trimester)	1-10 days; 11-35 days; >35 days Some heavy alcohol use; Frequent heavy alcohol use	ADHD	maternal interview - the Diagnostic Interview for Children and Adolescents (DICA)	recruitment over 2 years - 13, 15, 17 and 19 years	zygosity, prenatal and parental predictors - low birth weight, maternal alcohol abuse/dependence, paternal alcohol dependence	**OR (95% CI)** 1-10 days: 1.11 (0.72, 1.71) 11-35 days: 0.97 (0.26, 3.64) >35 days: 3.31 (0.83, 13.12) Some heavy alcohol use: 2.20 (0.95, 5.09) Frequent heavy alcohol use: 4.64 (1.40, 15.50)

Caffeine												
Del-Ponte et al., 2016	Brazil	population based longitudinal cohort study (Pelotas birth cohort study)	142/3485	both (reported separately for boys and girls)	11 years	Prospective interview after child's birth (assessed each trimester and throughout pregnancy)	<100 mg/day (ref); 100-299 mg/day; >300 mg/day	ADHD	The Development and Well-Being Assessment Scale (DAWBA) reported by mothers and diagnosis by a child psychiatrist	3, 12, 24 and 48 months, 6 and 11 years (ongoing study)	National Economic Index mother's and father's education levels, evaluated as years of study; maternal age, mother living with or without partner; number of cigarettes smoked per day by the mother during pregnancy; number of cigarettes smoked per day by the father in the mother's presence during pregnancy; alcohol consumption by the mother during pregnancy; number of antenatal care consultations; mood symptoms during pregnancy; maternal nutritional state before pregnancy, evaluated according to the body mass index (BMI); the child gestational age at birth; birth weight and sex	**OR (95% CI)** 1st trimester total sample 100-299 mg/day: 1.04 (0.62, 1.73) >300 mg/day: 0.93 (0.55, 1.60) Boys 100-299 mg/day: 1.06 (0.57, 1.98) >300 mg/day: 1.06 (0.57, 1.96) Girls 100-299 mg/day: 1.13 (0.44, 2.90) >300 mg/day: 0.68 (0.21, 2.17) 2nd trimester total sample 100-299 mg/day: 1.03 (0.61, 1.74) >300 mg/day: 0.95 (0.55, 1.63) Boys 100-299 mg/day: 1.03 (0.55, 1.94) >300 mg/day: 1.09 (0.58, 2.03) Girls 100-299 mg/day: 1.24 (0.48, 3.22) >300 mg/day: 0.75 (0.24, 2.38) 3rd trimester total sample 100-299 mg/day: 0.96 (0.55, 1.68) >300 mg/day: 1.05 (0.61, 1.81) Boys 100-299 mg/day: 0.82 (0.40, 1.68) >300 mg/day: 1.07 (0.57, 2.02) Girls 100-299 mg/day: 1.68 (0.64, 4.40) >300 mg/day: 1.22 (0.41, 3.60) Entire pregnancy

											<u>total sample</u> 100-299 mg/day: 1.12 (0.68, 1.84) >300 mg/day: 0.90 (0.51, 1.59) <u>Boys</u> 100-299 mg/day: 1.05 (0.57, 1.92) >300 mg/day: 1.01 (0.52, 1.95) <u>Girls</u> 100-299 mg/day: 1.46 (0.58, 3.68) >300 mg/day: 0.82 (0.25, 2.65)
Linnet et al., 2008	Denmark	population-based longitudinal cohort study (the Aarhus Birth Cohort)	88/24,068	both	7 years	prospective self-report (assessed during the 2nd pregnancy trimester)	No coffee (ref): 1-3 cups; 4-9 cups; 10+ cups	ADHD	Diagnosis was obtained from the Danish Psychiatric Case Register	up to age 12 years	prenatal smoking and alcohol use, maternal age, gender of the child, parental years of schooling after basic school, employment status, cohabitant status and parental and siblings' psychiatric hospitalisations or contacts in outpatient clinics	**OR (95% CI)** 1-3 cups: 0.9 (0.5, 1.6) 4-9 cups: 1.3 (0.7, 2.3) 10+ cups: 2.3 (0.9, 5.9)
Russell et al., 2015	USA	cross-sectional study (household survey in general population)	-/5924	both (reported separately for boys and girls)	15.3 years	retrospective self-report (pregnancy trimester not specified)	None to less than one cup per day; One or more cups per day	ODD	Structured diagnostic interview (CIDI - The World Health Organization's Composite International Diagnostic Interview)	NA	child age	**OR (95% CI)** Total sample: 0.86 (0.7, 1.0) Boys: 0.98 (0.8, 1.3) Girls: 0.75 (0.6, 1.0), p=<0.05* **coding unclear (authors are reporting increasing effect on ODD of caffeine use in girls)*

Appendix 2.8. Study characteristics and results of case-control studies

Author/Year	Country	Study sample	Cases/controls	Gender	Offspring age at assessment	Exposure assessment	Classification of exposure	Outcome	Outcome assessment	Follow up time	Confounders	Results (as reported in the study)
Smoking												
Biederman et al., 2009	USA	longitudinal case-control family study (clinical population)	291/536	both	13.2 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD CD	Clinical interview (K-SADS-E and SCID) with mothers and offspring, diagnosis confirmed by a psychiatrist	Assessments at baseline, 4 and 10 years for boys and in 5 years in girls. Age range at baseline 5 – 37 years (mean 13.4 years)	maternal age at offspring birth, social class, offspring age at baseline, offspring gender, parental lifetime history of ADHD, parental lifetime history of CD, prenatal exposure to maternal alcohol or illicit drugs, study of origin (Boys ADHD, Girls ADHD), referral status, number of assessments (ADHD analyses were adjusted for CD and vice versa)	**OR (95% CI), p-value** ADHD: 2.5 (1.39, 4.51), 0.002 CD: 3.3 (1.23, 8.88) **the association with CD was only among siblings from control families. No association was observed among siblings of ADHD families*
Gard et al., 2016	USA	longitudinal case-control (clinical and community sample)	140/88	only girls	20 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD hyperactive-impulsive and inattention subtype	Diagnostic interview (DISC-IV) with mothers as well as maternal and self-report on ADHD symptom domains (diagnosis based on DSM-IV criteria)	2 waves – 5 (mean age 14 years) and 10 years (mean age 20 years)	SES, maternal education, income, maternal ADHD, participant ODD symptoms and substance use **cases and controls matched by age and ethnicity*	**Beta, p-value** <u>Maternal report:</u> HYP: 0.16, 0.03 INA: 0.10 <u>Self-report:</u> HYP: 0.13, 0.08 INA: 0.09
Gustafsson and Kallen, 2010	Sweden	Population-based case-control registry study	229/32,012	Both	8-12 years	prospective self-report during antenatal visit (pregnancy trimester not specified)	No smoking; <10 cigarettes/day; >10 cigarettes/day	ADHD	Diagnosis derived from the hospital database (the department of child and adolescent psychiatry in Malmo)	from 5 up to 17 years	birth year, maternal age, birthplace, preterm birth, Apgar score, gestational age, child gender	**OR (95% CI), p-value** 1.35 (1.14, 1.6)
Joelsson et al., 2016	Finland	population-based nested case-control registry study	3136/50,550	Both	not specified	Prospective self-report to maternity clinic during 2nd pregnancy trimester	Non-smokers; Smoking only 1st trimester; Smoking after 1st trimester (analyses with binary exposure)	ADHD (with and without comorbid CD/ODD cases)	the Finnish Hospital Discharge Register (FHDR)	not specified	maternal and paternal psychiatric history, maternal history of any substance use, maternal and paternal age at birth of offspring, maternal and paternal immigrant status, maternal socioeconomic status (SES), birth weight for gestational age, Apgar scores at 1 min, number of previous births and gestational age **cases and controls matched by date of birth, sex and residence in Finland*	**OR (95% CI)** 1.59 (1.43, 1.77)

Linnet et al., 2005	Denmark	nested case-control registry study	170/3935	both	5.5 years	Prospective self-report collected by midwives during antenatal visit (pregnancy trimester not specified)	Binary (Yes/No)	Hyperkinetic disorder	Diagnosis were obtained from the Danish Psychiatric Central Register	up to 8 years	maternal, paternal, and siblings' psychiatric hospitalizations and outpatient contacts, socioeconomic factors, and maternal age **cases and control subjects were matched for age, gender, and calendar time*	**Relative Risk (RR) (95% CI)** 1.9 (1.3, 2.8)
Milberger et al., 1996	USA	case-control family study (clinical population)	140/260	only boys	6-17 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Structured interviews with mothers and offspring's using the childhood version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Epidemiologic Version (K-SADS-E). Diagnosis were confirmed by the psychiatrist	not specified	socioeconomic status, parental ADHD status, and parental IQ **cases and controls matched by ethnicity, gender and age*	**OR (SE), (95% CI), p-value** 2.7 (1.31), (1.1, 7.0), 0.04
Milberger et al., 1998	USA	case-control family study (clinical population) siblings of ADHD and non-ADHD families	174/300	both	13.5 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Structured interviews with mothers and offspring's using the childhood version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Epidemiologic Version (K-SADS-E). Diagnosis were confirmed by the psychiatrist	not specified	socioeconomic status, parental ADHD status, and parental IQ **cases and controls matched by ethnicity, gender and age*	**OR (SE), (95% CI), p-value** 4.4 (2.8), (1.2, 15.5), 0.02
Schmitz et al., 2006	Brazil	case-control	100/200	both	11.8 years	retrospective interview (pregnancy trimester not specified)	No smoking (ref); 1-9 cigarettes/day; >10 cigarettes/day	ADHD inattention subtype	3 stage process: The first stage was a semi-structured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version [K-SADS-E] administered to the parents. In stage 2, each diagnosis derived from the K-SADS-E was discussed in a clinical committee chaired by an experienced child and adolescent psychiatrist. For the third stage, a clinical evaluation of ADHD-I and comorbid conditions using DSM-IV criteria was conducted by a child and adolescent psychiatrist who previously received the results of the K-SADS-E and conducted interviews with the parents and the child or adolescent.	NA	maternal age, SES, maternal ADHD, child ODD, alcohol use in pregnancy, birth weight **cases and controls matched by gender and age*	**OR (95% CI), p-value** No smoking (ref) 1-9 cigarettes: 1.09 (0.32, 3.66), 0.89 >10 cigarettes: 3.44 (1.17, 10.06), 0.02
Silva et al., 2014	Australia	population-based case-control record linkage study	12,911/43,062	Both (reported separately for boys and girls)	<25 years	Prospective self-report collected by midwives during antenatal visit (pregnancy	Binary (Yes/No)	ADHD	stimulant medication for ADHD identified through the Monitoring of Drugs of Dependence System (MODDS). Controls were selected from the Midwives Notification	up to 25 years	marital status, parity, pregnancy complications, onset of labour, complications of labour, type of delivery, child	**OR (95% CI)** Boys: 1.86 (1.53, 2.27) Girls: 1.67 (1.07, 2.61)

						trimester not specified)			System (MNS) and matched by birth year, gender and SES		gestational age, birth weight *cases and controls matched by year of birth, gender and SES	
Todd et al., 2007	USA	case-control (population-based twin study, MOTWIN)	198/1518	both	13 years	retrospective self-report (assessed each pregnancy trimester)	Binary (Yes/No)	ADHD combined and inattentive subtype	Parents interview using the Missouri Assessment of Genetics Interview for Children (MAGIC) to obtain DSM-IV diagnoses and individual symptom information.	NA	child gender, negative expressed emotion in the family and DSM-IV diagnoses of oppositional defiant disorder (ODD) and conduct disorder (CD)	**OR (95% CI)** $ADHD_{combined}$: 3.9 (1.2, 13.1) **the association was observed between prenatal smoking and child genotype at the rs1044396 C allele (CHRNA4 gene) **Association was also observed between prenatal smoking and two genes (CHRNA4 and DAT1) - $ADHD_{comb}$ OR=6 (1.2, 28.9)*
Yoshimasu et al., 2009	Japan	case-control (hospital-based population)	90/360	both	10 years	retrospective interview (pregnancy trimester not specified)	Lifetime non-smokers (ref); Former smokers; Stopped smoking when aware of pregnancy; Continued smoking	ADHD	experienced psychiatrists or paediatricians diagnosed ADHD according to the diagnostic criteria of DSM-IV, with full consideration of both parents' and teachers' evaluations.	NA	children's gender, family income, maternal drinking during pregnancy, pregnancy-induced hypertension, birth weight, and children's iron intake, maternal tendency of ADHD, parental history of mental disorders and maternal mental stress during pregnancy **cases and controls matched by age*	**OR (95% CI)** Lifetime non-smokers (ref) Former smokers: 0.8 (0.3, 2.5) Stopped smoking: 1.3 (0.5, 3.6) Continued smoking: 1.3 (0.5, 3.6)
Altink et al., 2009	the Netherlands (the International Multi-centre ADHD Gene project (IMAGE))	case-control family study	79/184	both	12 years	retrospective self-report (assessed each pregnancy trimester)	Binary (Yes/No)	ADHD	All probands were included after completing clinical evaluations by a paediatrician or child psychiatrist prior to the study. The clinical diagnosis of the ADHD probands and siblings was verified with the Parental Account of Childhood Symptoms (PACS) by a trained interviewer	NA	Child age, gender, IQ, birth weight, oppositional and anxious-shy symptoms of a child, total maternal or paternal ADHD symptoms, maternal age and socio-economic status	**OR (95% CI), p-value** *association between maternal prenatal smoking and ADHD status 3.29 (1.48, 7.30), 0.003 This relationship was partly mediated by the performance on attentional control: OR=2.42, 95%CI 1.04, 5.61), p=<0.001 **no effect was found between prenatal smoking and child genotype on attentional control in children with ADHD* **paternal risk genes (DRD4, DAT1) mediated paternal smoking and effect on attentional control in children with ADHD*

Altink et al., 2008	Multiple countries (Belgium, Germany, Ireland, Spain, Switzerland, the Netherlands and UK) (IMAGE study)	case-control family study	539/946	both	11 years	retrospective self-report (assessed each pregnancy trimester)	Binary (Yes/No)	ADHD	All probands were included after completing clinical evaluations by a paediatrician or child psychiatrist prior to the study. The clinical diagnosis of the ADHD probands and siblings was verified with the Parental Account of Childhood Symptoms (PACS) by a trained interviewer	NA	child gender, age and birth weight	**OR (95% CI), p-value** *association between prenatal smoking and ADHD status: 1.76 (1.09, 2.85), 0.021 **no interaction effect was found between DRD4 gene and prenatal smoking 1.86 (0.69, 4.98)*
Neuman et al., 2007	USA	case-control (population-based twin study) (MOTWIN sample)	140/832	both	13 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD combined and inattentive subtype	1st stage - screening interview 2nd stage - diagnostic interview completed by parents (the Missouri Assessment of Genetics Interview for Children (MAGIC), a modified version of the Diagnostic Interview for Children and Adolescents)	NA	Child's gender, negative home environment, ODD and CD diagnosis	**OR (95% CI)** Any ADHD: 1.58 (1.03, 2.43) ADHD combined: 1.91 (0.97, 3.76) ADHD inattention: 1.52 (0.89, 2.58) **The odds for a diagnosis of DSM-IV ADHD was 1.8 times greater in twins whose genotype at the DAT3= VNTR contained the 440 allele and whose mother smoked during pregnancy than for twins who had neither risk factor. Similarly, the risk for a diagnosis of DSM-IV ADHD was significantly elevated in twins with prenatal smoke exposure and the DRD4 seven-repeat allele. There were no significant interactions for the DSM-IV ADHD phenotype between prenatal smoking and the DAT1 480 allele*
Arnold et al., 2005	USA	case-control (the Multimodal Treatment Study of Children with ADHD)	164/461	both	7-9.9 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	diagnosed prior to the study by the clinician	14 months	Child sex, mother's educational level, public assistance, single parent status, prenatal drinking, family history of ADHD and CD	**p-value** *prenatal smoking predicted ADHD status ADHD with comorbid CD/ODD: 0.024 ADHD without comorbidities: 0.096 **No moderating effect was found between prenatal smoke exposure and ADHD treatment outcome*
Biederman et al., 2017	USA	case-control (family study clinical population)	496 267 ADHD cases 115 CD cases 211 ODD cases"	both	21 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	CD ODD	The assessment had 3 stages: referral; telephone questionnaire with mother; diagnostic interview (DISC)	10 years for boys and 11 years for girls	SES, child ADHD **cases and controls matched by gender and age*	**OR (95% CI), p-value** CD: 1.51 (0.66, 1.96), 0.13 ODD: 1.14 (0.66, 1.96), 0.63

Ketzer et al., 2012	Brazil	case-control	124/248	both	11.8 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD inattention subtype	3 stage assessment: 1st stage – a semi-structured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children) modified to assess DSM-IV criteria and administered to the parents by trained research assistants 2nd stage - each diagnosis derived from the K-SADS-E was discussed in a clinical committee chaired by an experienced child and adolescent psychiatrist 3rd stage - a clinical evaluation of ADHD-I and comorbid conditions were performed according to DSM-IV criteria by a child and adolescent psychiatrist who previously had access to K-SADS-E results.	NA	generalised anxiety disorder, ODD, agoraphobia, maternal ADHD. *Cases and controls were matched by age and gender	**OR (95% CI), SE, p-value** 1 (0.9, 1.1), 0.03, 0.2
Mick et al., 2002	USA	case-control family study (clinical population)	280/522	both	11 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	structured diagnostic interview (the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version (K-SADS-E). All assessments were made by raters who were blind to the child's diagnosis (ADHD or non-ADHD control) and ascertainment site	NA	maternal age at child's birth, indicators of social adversity (low social class, large family size, severe marital discord), parental history of ADHD, parental history of CD/ASPD, and comorbid CD in cases and controls *cases and controls matched by gender and age	**OR (95% CI), p-value** 2.1 (1.1, 4.1), 0.02
Pineda et al., 2007	Columbia	case-control	200/486	both	8.3 years	retrospective self-report (pregnancy trimester not specified)	No smoking (ref); Low: 1-3 cigarettes/day; High: 4+ cigarettes/day	ADHD	psychiatric Diagnostic Interview for Children and Adolescents—parent revised Spanish version (DICA-PR). DSM-IV-ADHD-symptoms questionnaire, Behavioural Assessment System for Children (BASC) - parent and teacher report. All psychiatric, medical, neurological, neuropsychological, and psychological records of the ADHD children were reviewed by neurologists and neuro-psychologists. Parents provided information about the current clinical condition of their children and filled out the ADHD retrospective structured risk factor survey.	NA	gender and school grades *cases and controls matched by age, SES and school level	**OR (95% CI), p-value** High: 8.9 (1.0, 78.4), <0.05
Motlagh et al., 2010	USA	case-control	52/117	both	11.8 years	retrospective interview	Binary (>10 cigarettes/day/No)	ADHD	Semi-structured interview using the Schedule for Affective	NA	gender, severe psychosocial stress and limited coping	**OR (95% CI), p-value** 18.6 (2.1, 164.4), 0.008

						(pregnancy trimester not specified)			Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (SADS-PLV) and a ''best estimate'' consensus procedure in which expert clinicians considered all available clinical and diagnostic information		abilities during pregnancy, more than one pregnancy complication, and antibiotic use *cases and controls matched by age and ZIP code	
Wiggs et al., 2016	USA	case-control family study	251/464	both	11 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD (hyperactivity-impulsivity and inattention) CD ODD	Schedule for Affective Disorders and Schizophrenia-E for each child with a trained master's level clinical interviewer. Clinical data were reviewed, and a best estimate diagnostic procedure was implemented by a board-certified child psychiatrist and a licensed child clinical psychologist	NA	child sex, age, ethnicity, income, parental ADHD symptoms and externalizing disorder status, and maternal and paternal age at birth	**Beta(β), 95% CI, p-value** Direct effect of prenatal tobacco exposure INA: 0.05 (-0.01, 0.11), 0.19 HYP: 0.03 (-0.05, 0.11), 0.56 CD: 0.02 (-0.08, 0.12), 0.76 ODD: 0.04 (-0.06, 0.14), 0.19 **Indirect effect of prenatal tobacco exposure via neuropsychological functioning INA: 0.08 (0.02, 0.14), 0.02 specifically via memory span β=.03, (0.005, 0.06], p=. 039 *indirect effects were observed also for CD β=.04, (0.005, 0.07], p=.060 and ODD β=.04, (0.00, 0.07], p=.08*
Oerlemans et al., 2016	the Netherlands (the International Multi-centre ADHD Gene project (IMAGE))	case-control family study	201/768	both	11.2 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Conners rating scale; Parental Account of Childhood Symptoms ADHD subversion and diagnostic interview	NA	Family size, parity, child gender	**OR (95% CI), p-value** 2.12 (1.52, 4.48), 0.005 **single and multiple ADHD incidence stratification showed that prenatal smoking was a shared familial risk between affected and unaffected ADHD children*
Alcohol												
Ketzer et al., 2012	Brazil	case-control	124/248	both	11.8 years	retrospective self-report (pregnancy trimester not specified)	Binary (Yes/No)	ADHD inattention subtype	3 stage assessment: 1st stage – a semi-structured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children) modified to assess DSM-IV criteria and administered to the parents by trained research assistants 2nd stage - each diagnosis derived from the K-SADS-E was discussed in a clinical committee chaired by an experienced child and adolescent psychiatrist 3rd stage - a clinical evaluation of ADHD-I and	NA	social phobia, ODD, maternal ADHD, IQ, tobacco use in pregnancy **cases and controls matched by age and gender"*	**OR (95% CI), SE, p-value** 3.2 (0.8, 12.6), 0.7, 0.1

									comorbid conditions were performed according to DSM-IV criteria by a child and adolescent psychiatrist who previously had access to K-SADS-E results.			
Mick et al., 2002	USA	case-control family study (clinical population)	280/522	both	11 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	structured diagnostic interview (the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version (K-SADS-E). All assessments were made by raters who were blind to the child's diagnosis (ADHD or non-ADHD control) and ascertainment site	NA	maternal age at child's birth, indicators of social adversity (low social class, large family size, severe marital discord), parental history of ADHD, parental history of CD/ASPD, and comorbid CD in cases and controls	**OR (95% CI), p-value** 2.5 (1.1, 5.5), 0.03
Pineda et al., 2007	Columbia	case-control	200/486	both	8.3 years	retrospective self-report (pregnancy trimester not specified)	No drinking (ref); Low: <10 drinks/week High:Drunkenness during the first 2 months	ADHD	psychiatric Diagnostic Interview for Children and Adolescents—parent revised Spanish version (DICA-PR). DSM-IV-ADHD-symptoms questionnaire, Behavioural Assessment System for Children (BASC) - parent and teacher report. All psychiatric, medical, neurological, neuropsychological, and psychological records of the ADHD children were reviewed by neurologists and neuro-psychologists. Parents provided information about the current clinical condition of their children and filled out the ADHD retrospective structured risk factor survey.	NA	gender and school grades **cases and controls matched by age, SES and school level.*	**OR (95% CI), p-value** High: 11.7 (1.5, 94.1), 0.02
Kim et al., 2009	Korea	case-control	100/2319	both	10.5 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Psychiatric disorders were assessed, according to the Diagnostic and Statistical Manual of Mental Disorders 4th version (DSM-IV), with the Korean version of the DISC-IV and with parental interview	NA	age, gender, SES (by income)	**OR (95% CI)** 3.31 (1.59, 6.91)
Caffeine												
Kim et al., 2009	Korea	case-control	100/2319	both	10.5 years	retrospective interview (pregnancy trimester not specified)	Binary (Yes/No)	ADHD	Psychiatric disorders were assessed, according to the Diagnostic and Statistical Manual of Mental Disorders 4th version (DSM-IV), with the Korean version of the DISC-IV and with parental interview	NA	age, gender, SES (by income)	**OR (95% CI)** 1.28 (0.81, 2.02)

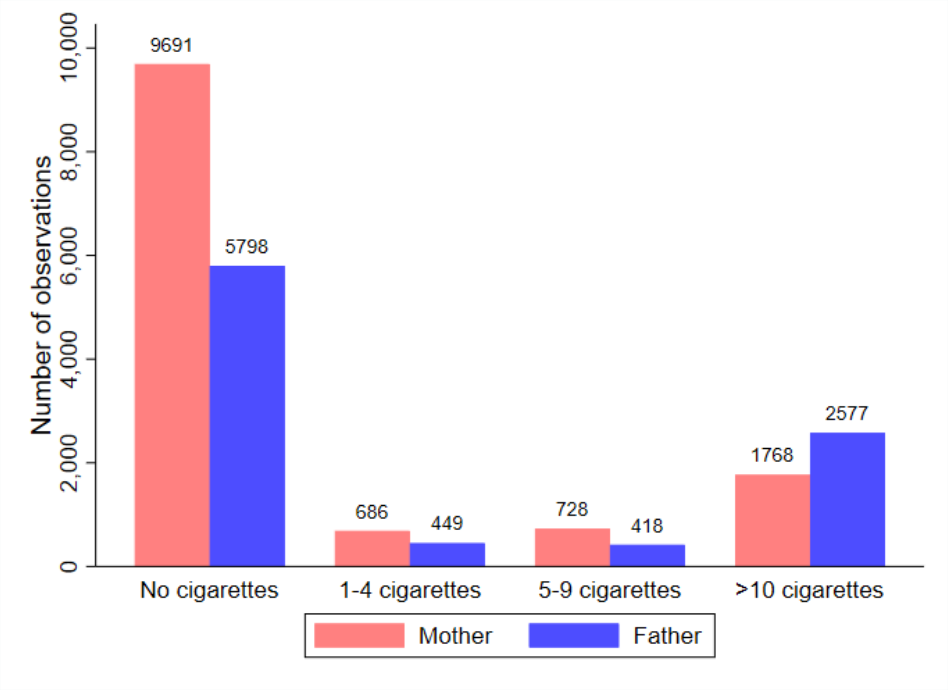
Appendix 2.9. Confounders included in the cohort, longitudinal and cross-sectional studies

Number of studies adjusted for this confounder			
Confounder	**Tobacco** (28 studies)	**Alcohol** (9 studies)	**Caffeine** (3 studies)
Offspring gender	21 (75%)	7 (78%)	2 (67%)
Offspring age	18 (64%)	6 (67%)	1
Offspring ethnicity	9 (32%)	4 (44%)	-
Offspring comorbid externalising disorders	-	-	-
Parity and/or number of siblings	9 (32%)	2 (22%)	
Maternal age at offspring birth	17 (61%)	3 (33%)	2 (67%)
Parental socio-economic characteristics (social class, education, income, marital status)	21 (75%)	7 (78%)	2 (67%)
Parenting behaviour and/or home environment	5 (18%)	4 (44%)	-
Parental externalising disorder symptoms (ADHD, antisocial personality)	3 (11%)	-	-
Other parental psychopathology and substance use disorders	13 (46%)	4 (44%) 1	1
Maternal mental health during pregnancy	2 (7%)	-	1
Maternal other substance use during pregnancy	10 (36%)	4 (44%)	2 (67%)
Household member substance use during pregnancy	1 (4%)	-	-
Perinatal factors (birth weight, gestational age, birth complications)	14 (50%)	4 (44%)	1

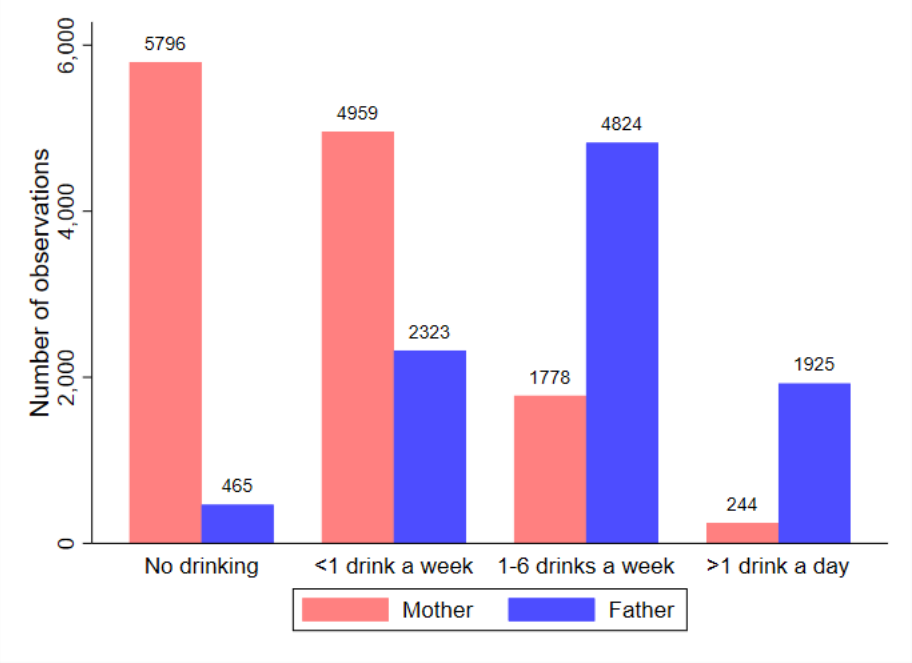
Appendix 2.10. Confounders included in the case-control studies

Number of studies adjusted for this confounder			
Confounder	**Tobacco** (22 studies)	**Alcohol** (4 studies)	**Caffeine** (1 study)
Offspring gender	21 (95%)	3 (75%)	1
Offspring age	17 (77%)	3 (75%)	1
Offspring ethnicity	5 (23%)	-	-
Offspring comorbid externalising disorders	9 (41%)	2 (50%)	
Parity and/or number of siblings	3 (14%)	-	-
Maternal age at offspring birth	8 (36%)	1	
Parental socio-economic characteristics (social class, education, income, marital status)	15 (68%)	4 (100%)	1
Parenting behaviour and/or home environment	2 (9%)	-	-
Parental externalising disorder symptoms (ADHD, antisocial personality)	11 (50%)	2 (50%)	-
Other parental psychopathology, and substance use disorders	3 (14%)	-	-
Maternal mental health during pregnancy	2 (9%)	-	-
Maternal other substance use during pregnancy	5 (23%)	1	
Partner's substance use during pregnancy	-	-	-
Perinatal factors (birth weight, gestational age, birth and pregnancy complications)	8 (36%)	-	-

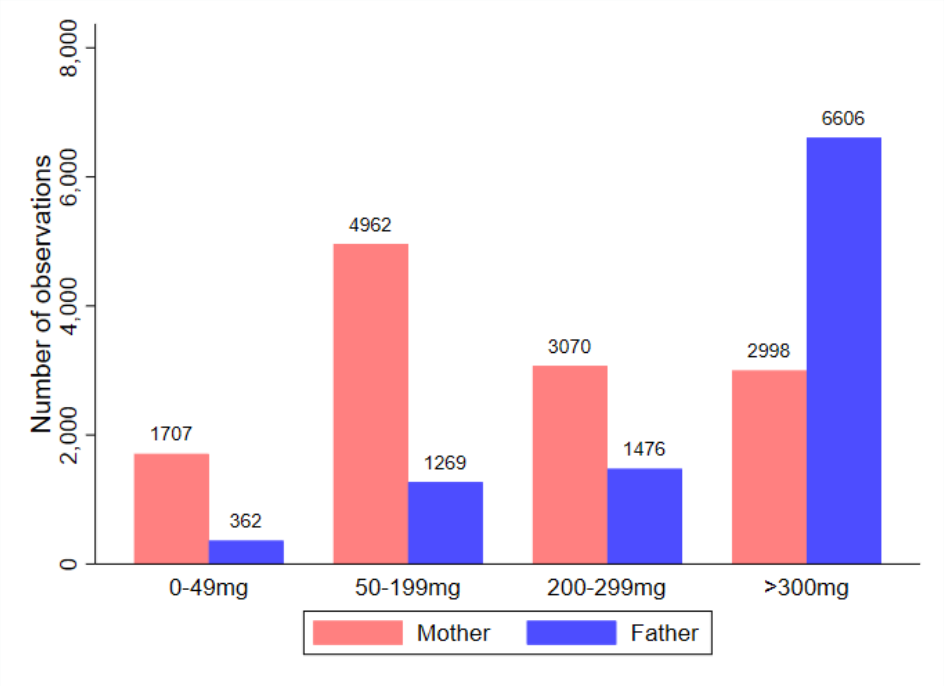
Appendix 3.1. Maternal and paternal daily smoking during the 1st pregnancy trimester in ALSPAC



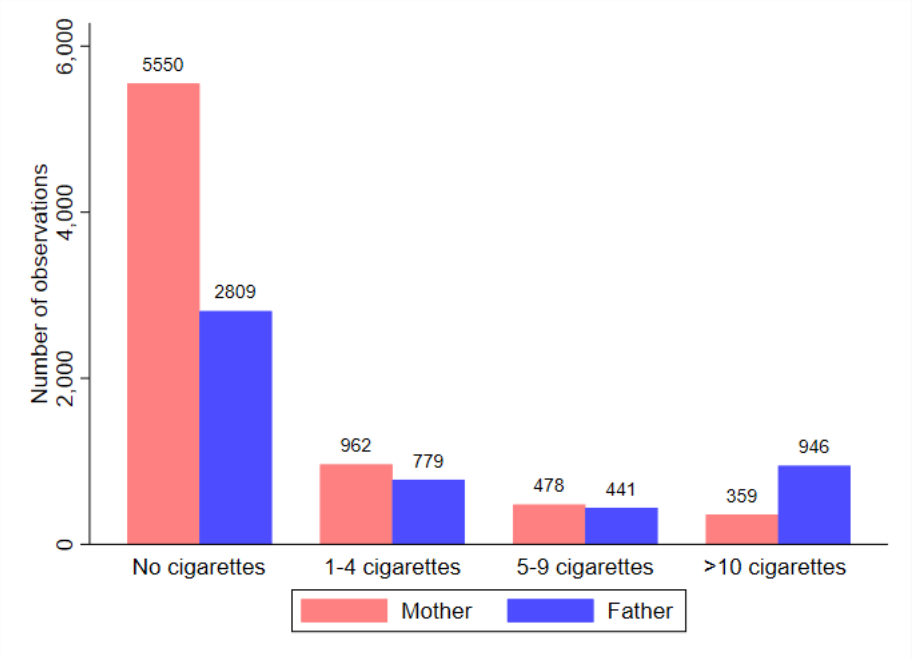
Appendix 3.2. Maternal and paternal alcohol consumption during the 1st pregnancy trimester in ALSPAC



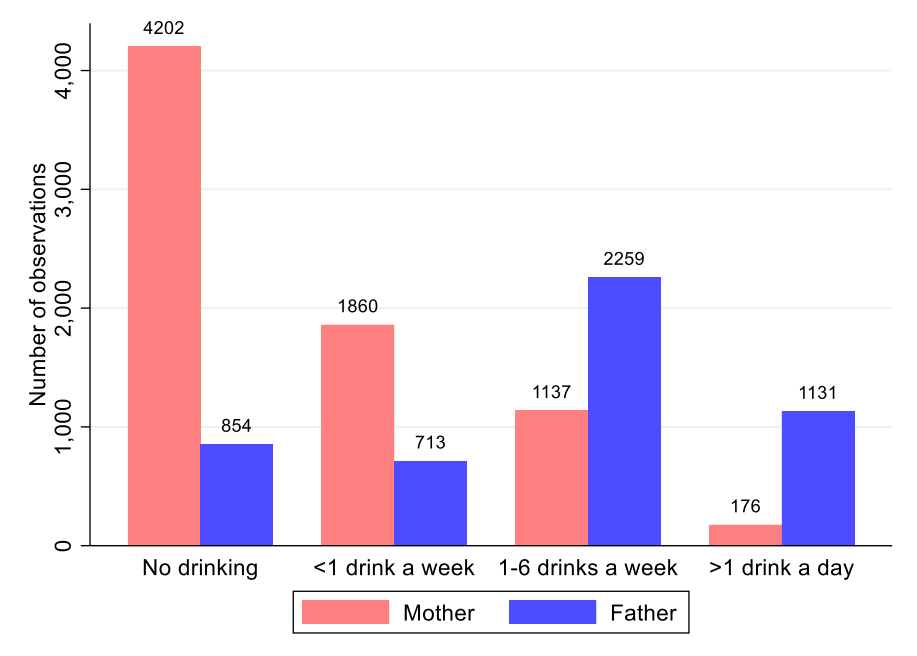
Appendix 3.3. Maternal and paternal daily caffeine consumption during the 1st pregnancy trimester in ALSPAC



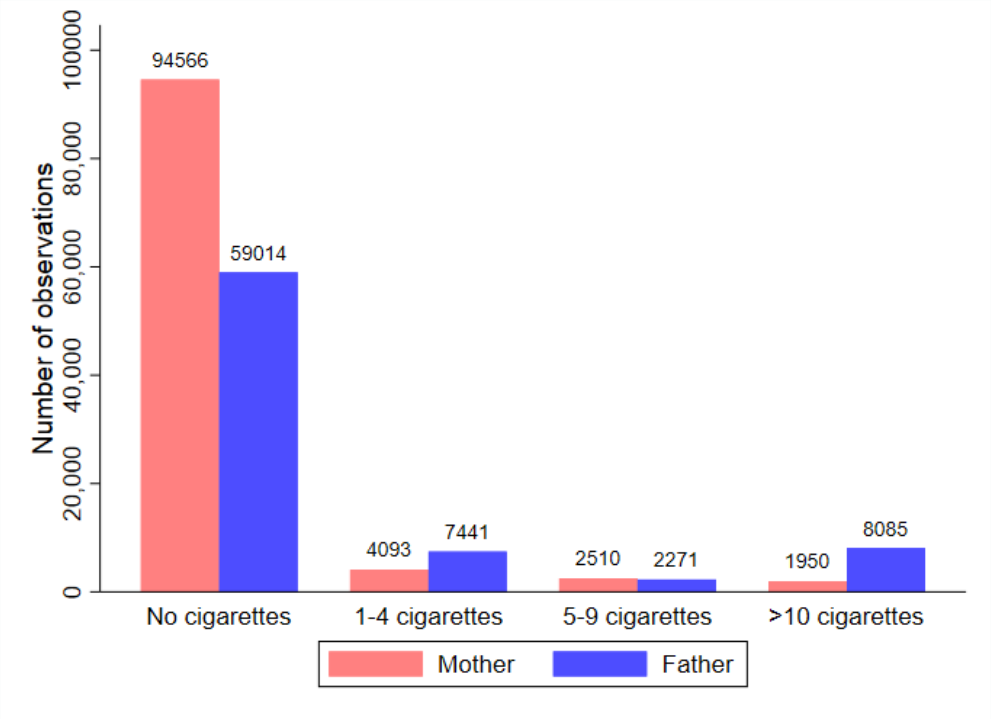
Appendix 3.4. Maternal and paternal daily smoking during the 1st pregnancy trimester in GenR



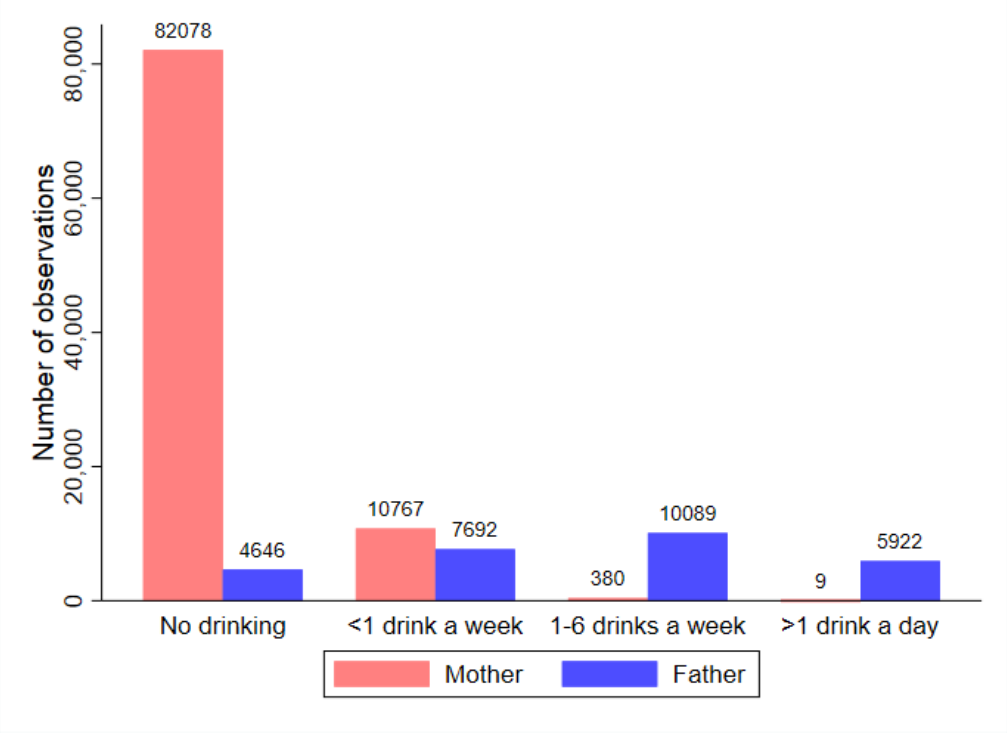
Appendix 3.5. Maternal and paternal alcohol consumption during the 1st pregnancy trimester in GenR



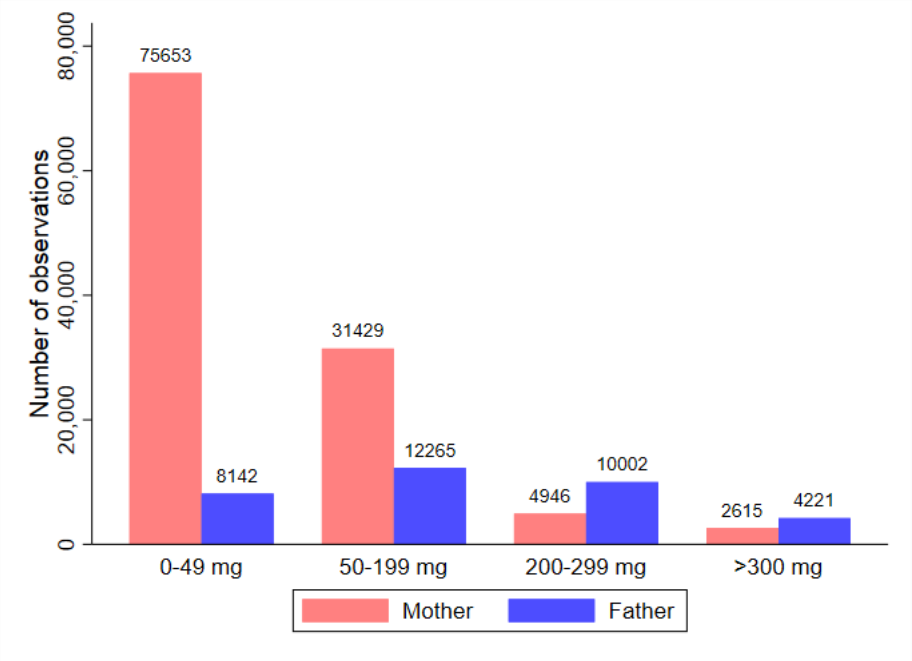
Appendix 3.6. Maternal and paternal daily smoking during the 1st pregnancy trimester in MoBa



Appendix 3.7. Maternal and paternal alcohol consumption during the 1st pregnancy trimester in MoBa



Appendix 3.8. Maternal and paternal daily caffeine consumption during the 1st pregnancy trimester in MoBa



Appendix 4.1. Associations between maternal and offspring lifetime smoking PRSs and smoking phenotypes in mothers and adolescence

Phenotype	Effect estimate	Effect size*	95% CI	P-value	Sample size	R^2
Mothers during pregnancy						
Tobacco smoked in 1st three months of pregnancy	OR	1.24	1.159, 1.315	$9.41x10^{-6}$	7,237	0.04
Mother cut down tobacco consumption	OR	1.17	1.097, 1.244	<0.001	7,269	0.02
Mother stopped smoking during pregnancy	OR	0.87	0.775, 0.979	0.024	1,863	0.01
Mothers outside of pregnancy						
Mother has ever smoked	OR	1.15	1.089, 1.209	<0.001	7,194	0.01
Number of cigarettes mother smoked before pregnancy	Beta	0.19	0.124, 0.264	$5.27x10^{-8}$	3,426	0.05
Number of cigarettes smoked last 2weeks	Beta	0.76	0.191, 1.318	0.011	845	
Offspring: Adolescents						
Smoked age 14 years	OR	1.12	1.033, 1.208	0.009	4,145	0.03
Smoked more than 20 cigarettes age 14	OR	1.16	0.995, 1.342	0.057	1,058	0.01
Age 1st smoked a cigarette (asked age 14)	Beta	-0.05	-0.096, -0.009	0.019	1,064	0.01
Ever smoked a whole cigarette age 18	OR	1.13	1.035, 1.233	0.010	2,402	0.01
Number of cigarettes smoked in lifetime age 18	Beta	0.08	-0.004, 0.171	0.061	1,144	0.002

*Note: *Reflects the average change in the outcome that is associated with a one standard deviation increase in the PRS. For binary outcomes, this will be the odds ratio (OR) (eg Mother's odds of ever smoking are 1.2 times compared to not smoking), for continuous outcomes it represents the average unit change (eg 0.2 cigarettes smoked); 95% CI – 95% confidence intervals; R^2 – variance explained by the PRS*

Appendix 4.2. Associations between maternal smoking initiation PRS and maternal outcomes during and outside of pregnancy

		Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Mothers during pregnancy							
Mental health							
Depression (18wks)	OR	1.12	1.028, 1.211	0.013	0.001, 0.010	0.004	6,734
Depression (32wks)	OR	1.12	1.039, 1.216	0.007	<0.001, 0.006	0.001	6,751
Anxiety	OR	1.00	0.915, 1.091	0.991	0.979, 0.994	0.988	6,645
Hypersensitivity to interpersonal rejection	Beta	-0.47	-0.846, -0.102	0.012	0.003, 0.016	0.008	7,167
Feelings becoming a parent	Beta	-0.003	-0.025, 0.018	0.752	0.724, 0.778	0.752	7,165
Substance use							
Caffeine							
Total caffeine (18wks)	Beta	7.35	4.748, 9.957	$3.25x10^{-8}$	<0.001, 0.004	<0.001	7,220
Total caffeine (32wks)	Beta	6.28	3.693, 8.872	$2.02x10^{-6}$	<0.001, 0.004	<0.001	6,767
Alcohol							
Binge drinking (18wks)	Beta	0.04	0.024, 0.061	$8.07x10^{-6}$	<0.001, 0.004	<0.001	7,171
Binge drinking (32wks)	Beta	0.03	0.014, 0.054	0.001	<0.001, 0.004	<0.001	5,324
Weekly alcohol units (32wks)	Beta	0.16	0.033, 0.286	0.013	0.003, 0.014	0.007	4,294
Other substances							
Cannabis use in pregnancy	OR	1.17	0.977, 1.389	0.082	0.046, 0.077	0.060	6,918
Hard drug use in pregnancy	OR	0.99	0.568, 1.726	0.971	0.947, 0.972	0.961	7,147
Non-mental health							
Education	Beta	-0.10	-0.128, -0.071	$1.01x10^{-11}$	<0.001, 0.004	<0.001	6,954
Social class	Beta	0.05	0.023, 0.078	$3.19x10^{-4}$	<0.001, 0.004	<0.001	5,854
Life events in pregnancy	Beta	0.05	0.018, 0.074	0.001	<0.001, 0.004	<0.001	6,744
Image perception in pregnancy	Beta	0.15	0.045, 0.245	0.005	0.004, 0.017	0.009	6,699
Image perception change	Beta	0.08	-0.011, 0.166	0.087	0.079, 0.117	0.097	6,549
Activity level compared with other pregnant women	Beta	0.01	-0.008, 0.029	0.262	0.226, 0.281	0.253	6,611
Physical activity	OR	1.01	0.951, 1.066	0.795	0.764, 0.816	0.795	6,767

Vomiting in first three months of pregnancy	OR	0.98	0.927, 1.034	0.418	0.367, 0.428	0.397	6,797
Sleep problems (18wks)	Beta	0.02	0.001, 0.036	0.036	0.015, 0.036	0.005	6,742
Sleep problems (32wks)	Beta	0.03	0.009, 0.046	0.003	<0.001, 0.004	<0.001	6,743
Mothers outside of pregnancy							
Mental health							
Depression symptoms	OR	1.07	0.969, 1.182	0.161	0.117, 0.161	0.138	4,725
Anxiety symptoms	OR	1.03	0.934, 1.131	0.542	0.515, 0.577	0.546	4,740
Bulimia	OR	1.08	0.926, 1.261	0.295	0.319, 0.379	0.349	6,799
Drug addiction	OR	0.94	0.594, 1.480	0.764	0.748, 0.801	0.775	6,799
Alcoholism	OR	1.24	0.903, 1.711	0.163	0.118, 0.162	0.139	6,799
Schizophrenia	OR	0.84	0.386, 1.825	0.632	0.585, 0.646	0.616	6,799
Anorexia nervosa	OR	1.06	0.886, 1.272	0.484	0.429, 0.491	0.460	6,799
Severe depression	OR	1.18	1.064, 1.303	0.004	<0.001, 0.004	<0.001	6,799
Other psychological problem	OR	1.15	0.941, 1.396	0.157	0.103, 0.145	0.123	6,799
Substance use							
Alcohol							
Alcohol drinking before pregnancy	OR	1.13	1.017, 1.253	0.026	0.006, 0.020	0.011	7,199
Binge drinking	Beta	0.05	0.020, 0.080	0.001	<0.001, 0.004	<0.001	4,866
Daily alcohol units at child age 4	Beta	0.02	0.003, 0.044	0.027	0.018, 0.039	0.027	5,680
Daily alcohol units at child age 8	Beta	-0.003	-0.033, 0.027	0.838	0.799, 0.847	0.824	2,707
AUDIT score	Beta	0.02	0.002, 0.045	0.036	0.034, 0.061	0.046	2,424
Caffeine							
Total caffeine consumption	Beta	8.57	4.948, 12.187	<0.001	<0.001, 0.004	<0.001	4,783
Non-mental health							
Life events	Beta	0.02	-0.012, 0.055	0.212	0.222, 0.277	0.249	4,219
Sleep duration	Beta	-0.02	-0.049, 0.004	0.099	0.088, 0.127	0.106	1,867
Impulsivity personality trait	Beta	0.07	-0.034, 0.177	0.183	0.147, 0.195	0.170	4,847
Monotony avoidance personality trait	Beta	0.24	0.099, 0.386	0.001	<0.001, 0.006	0.001	4,794
Anger personality trait	Beta	0.34	0.207, 0.475	<0.001	<0.001, 0.004	<0.001	4,769
Suspicion personality trait	Beta	0.13	0.016, 0.234	0.024	0.012, 0.031	0.020	4,856
Detachment personality trait	Beta	-0.06	-0.169, 0.053	0.304	0.293, 0.352	0.322	4,753
Physical activity	OR	0.93	0.858, 1.014	0.094	0.040, 0.069	0.053	2,787

Social class	Beta	0.02	-0.024, 0.064	0.379	0.422, 0.484	0.453	2,906
Education	Beta	-0.09	-0.124, -0.060	2.19×10^{-8}	<0.001, 0.004	<0.001	4,919
BMI before pregnancy	Beta	0.21	0.117, 0.302	9.67×10^{-6}	<0.001, 0.004	<0.001	6,398
Image perception before pregnancy	Beta	0.06	0.029, 0.082	3.26×10^{-5}	<0.001, 0.004	<0.001	6,623

Note: OR-odds ratio; 95% CI – 95% confidence intervals

Appendix 4.3. Associations between offspring smoking initiation PRS and offspring outcomes in adolescence

		Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Offspring: Adolescents							
Mental health							
Conduct disorder symptoms	Beta	0.04	0.015, 0.066	0.002	<0.001, 0.006	0.001	3,834
ADHD symptoms	Beta	0.05	0.016, 0.085	0.004	0.001, 0.010	0.004	3,852
Oppositional-defiant disorder symptoms	Beta	0.04	0.011, 0.060	0.004	<0.001, 0.006	0.001	3,436
Psychosis positive symptoms age 12	Beta	0.02	<0.001, 0.029	0.046	0.034, 0.061	0.046	4,974
Psychosis negative symptoms age 16	Beta	-0.02	-0.059, 0.015	0.251	0.230, 0.285	0.257	3,511
Psychosis positive symptoms age 18	Beta	0.01	-0.004, 0.028	0.134	0.089, 0.129	0.134	3,403
PTSD disorder	Beta	0.01	-0.002, 0.028	0.085	0.042, 0.071	0.055	4,008
Depression score age 17 (MFQ)	Beta	0.01	-0.004, 0.020	0.178	0.164, 0.214	0.188	3,212
Depression symptom score age 18 (CIS-R)	Beta	0.02	-0.010, 0.041	0.236	0.210, 0.264	0.236	3,303
Eating disorder age 16	Beta	-0.002	-0.007, 0.002	0.281	0.247, 0.303	0.274	3,543
Eating disorder age 13	Beta	-0.001	-0.003, 0.001	0.395	0.452, 0.514	0.483	4,256
Specific phobia symptoms	Beta	0.01	-0.008, 0.028	0.298	0.269,0.326	0.297	3,293
Emotional problems symptoms	Beta	-0.01	-0.032, 0.014	0.422	0.410, 0.472	0.441	4,073
Self-harming behaviour	OR	0.96	0.810, 1.135	0.596	0.562, 0.624	0.593	2,576
Depression symptoms score age 14 (MFQ)	Beta	-0.002	-0.016, 0.013	0.821	0.808, 0.856	0.833	4,574
Anxiety score	Beta	0.002	-0.023, 0.027	0.848	0.830, 0.874	0.853	3,293
Total behavioural difficulties score	Beta	0.04	-0.001, 0.073	0.055	0.035, 0.062	0.047	4,055
Substance use							
Cannabis use	OR	1.23	1.127, 1.330	<0.001	<0.001, 0.004	<0.001	3,571
AUDIT risk score age 18	Beta	0.04	0.018, 0.064	0.001	<0.001, 0.004	<0.001	3,008
Binge drinking age 18	Beta	0.07	0.025, 0.114	0.002	0.001, 0.010	0.004	2,829
AUDIT total score age 18	Beta	0.07	0.029, 0.109	6.58×10^{-4}	<0.001, 0.004	<0.001	3,008
Number of alcoholic drinks on a typical day	Beta	0.07	0.022, 0.111	0.003	<0.001, 0.007	0.002	2,826
Number of drinks to feel tipsy	Beta	0.05	0.008, 0.093	0.020	0.017, 0.038	0.026	2,391

Number of drinks to feel different after first five times drinking	Beta	0.1	-0.016, 0.211	0.093	0.073, 0.109	0.090	299
Binge drinking age 13	Beta	0.04	-0.065, 0.142	0.461	0.421, 0.483	0.452	464
Frequency of having alcoholic drinks	Beta	0.01	-0.024, 0.039	0.641	0.586, 0.647	0.617	3,626
Number of times had whole drink age 13	Beta	0.01	-0.066, 0.079	0.860	0.838, 0.882	0.861	1,103
Frequency of cannabis smoking	Beta	-0.02	-0.092, 0.060	0.676	0.625, 0.684	0.655	1,035
Total caffeine age 13	Beta	0.01	-0.030, 0.046	0.680	0.639, 0.698	0.669	3,405
Non-mental health							
BMI	Beta	0.24	0.104, 0.373	0.001	<0.001, 0.004	<0.001	3,606
IQ	Beta	-0.58	-1.006, -0.159	0.007	0.003, 0.016	0.008	3,720
GCSE grades D-G	OR	1.09	0.988, 1.193	0.083	0.040, 0.069	0.053	2,182
GCSE grades A-C	OR	0.82	0.651, 1.032	0.085	0.063, 0.097	0.079	2,360
Extraversion personality trait	Beta	0.36	0.155, 0.569	0.001	<0.001, 0.006	0.001	4,354
Conscientiousness personality trait	Beta	-0.22	-0.403, -0.031	0.022	0.006, 0.021	0.012	4,162
Emotional Stability personality trait	Beta	-0.07	-0.263, 0.117	0.449	0.436, 0.498	0.467	4,224
Intellect personality trait	Beta	-0.05	-0.226, 0.119	0.545	0.491, 0.553	0.522	4,263
Agreeableness personality trait	Beta	-0.04	-0.188, 0.113	0.628	0.610, 0.671	0.641	4,279
Sleep maintenance	Beta	0.03	<0.001, 0.051	0.051	0.039, 0.068	0.052	3,418
Sleep initiation (time to fall asleep)	Beta	0.01	-0.027, 0.043	0.641	0.616, 0.677	0.647	3,626
Sleep duration (hours of sleep)	Beta	0.02	-0.017, 0.047	0.360	0.304, 0.363	0.333	3,726
Frequency of doing exercise	Beta	-0.004	-0.027, 0.020	0.762	0.736, 0.790	0.764	4,270
Life events	Beta	-0.01	-0.043, 0.031	0.756	0.762, 0.814	0.789	3,376

Note: OR - odds ratio; 95% CI – 95% confidence intervals

Appendix 4.4. Associations between maternal caffeine PRS and maternal outcomes during and outside of pregnancy

		Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Mothers during pregnancy							
Mental health							
Depression symptoms (18 wks)	OR	0.98	0.905, 1.067	0.647	0.616, 0.677	0.647	6,734
Depression symptoms (32 wks)	OR	0.99	0.920, 1.074	0.870	0.823, 0.869	0.847	6,751
Anxiety symptoms	OR	1.01	0.919, 1.099	0.910	0.891, 0.927	0.910	6,645
Hypersensitivity to interpersonal rejection	Beta	-0.04	-0.412, 0.322	0.833	0.838, 0.882	0.861	7,167
Feelings becoming a parent	Beta	0.01	-0.015, 0.030	0.528	0.496, 0.558	0.527	7,165
Substance use							
Tobacco							
Ever smoked in pregnancy	OR	1.01	0.947, 1.070	0.813	0.783, 0.833	0.809	6,718
Smoking first three months in pregnancy	OR	1.03	0.966, 1.097	0.343	0.275, 0.333	0.303	7,237
Caffeine							
Reduced caffeine consumption during pregnancy	OR	1.05	1.001, 1.111	0.046	0.017, 0.038	0.026	7,269
Reduced coffee consumption during pregnancy	OR	1.06	1.008, 1.117	0.028	0.006, 0.021	0.012	7,269
Stopped drinking cola during pregnancy	OR	1.09	0.991, 1.208	0.072	0.034, 0.061	0.046	4,570
Never drank coffee	OR	1.06	0.988, 1.146	0.093	0.059, 0.092	0.074	6,782
Never drank cola	OR	1.00	0.946, 1.062	0.933	0.915, 0.947	0.932	6,744
Stopped drinking coffee during pregnancy	OR	1.04	0.981, 1.100	0.175	0.104, 0.146	0.124	5,809
Never has been drinking caffeine	OR	0.97	0.918, 1.018	0.179	0.126, 0.170	0.147	7,269
Stopped drinking tea during pregnancy	OR	1.04	0.973, 1.109	0.226	0.184, 0.236	0.209	6,082
Reduced cola consumption during pregnancy	OR	1.04	0.967, 1.116	0.272	0.244, 0.300	0.271	7,269
Never drank tea	OR	1.04	0.950, 1.141	0.353	0.269, 0.326	0.297	6,754
Reduced tea consumption during pregnancy	OR	1.03	0.970, 1.085	0.333	0.290, 0.349	0.319	7,269
Consumed more caffeine during pregnancy	OR	1.04	0.948, 1.137	0.384	0.333, 0.394	0.363	7,269
No change in caffeine consumption during pregnancy	OR	0.99	0.934, 1.041	0.580	0.532, 0.594	0.563	7,269
Craved or had more caffeine during pregnancy	OR	0.99	0.909, 1.068	0.698	0.682, 0.739	0.711	7,269

Craved or had more coffee during pregnancy	OR	0.98	0.824, 1.160	0.774	0.700, 0.756	0.729	6,782
Craved or had more tea during pregnancy	OR	1.01	0.927, 1.108	0.750	0.718, 0.773	0.746	6,754
Alcohol							
Binge drinking (32wks)	Beta	-0.02	-0.04, -0.003	0.026	0.031, 0.057	0.043	5,324
Binge drinking (18wks)	Beta	-0.01	-0.03, 0.306	0.268	0.249, 0.306	0.277	7,171
Weekly alcohol units (32wks)	Beta	-0.06	-0.167, 0.056	0.329	0.314, 0.373	0.343	4,294
Craved or had more alcohol during pregnancy	OR	0.95	0.569, 1.584	0.828	0.826, 0.872	0.850	6,771
Other substances							
Cannabis use in first three months during pregnancy	OR	1.12	0.952, 1.328	0.151	0.134, 0.180	0.156	6,918
Hard drugs during pregnancy	OR	1.00	0.664, 1.491	0.980	0.968, 0.987	0.979	7,147
Non-mental health							
Life events during pregnancy	Beta	0.001	-0.028, 0.023	0.944	0.154, 0.202	0.177	6,930
Activity level compared with other pregnant women	Beta	0.01	-0.007, 0.029	0.234	0.227, 0.282	0.254	6,611
Image perception during pregnancy	Beta	-0.03	-0.029, 0.023	0.540	0.517, 0.579	0.548	6,699
Physical activity	Beta	-0.003	-0.021, 0.016	0.780	0.754, 0.806	0.781	6,767
Social class	Beta	0.03	0.001, 0.054	0.043	0.035, 0.062	0.047	6,954
Image perception change	Beta	0.02	-0.070, 0.108	0.678	0.394, 0.456	0.425	3,741
Education	Beta	-0.01	-0.034, 0.023	0.709	0.658, 0.717	0.688	6,954
Vomiting in first three months during pregnancy	OR	1.00	0.950, 1.059	0.903	0.871, 0.911	0.892	6,797
Sleeping problems (18 wks)	Beta	0.002	-0.015, 0.019	0.825	0.797, 0.845	0.822	6,742
Sleeping problems (32 wks)	Beta	-0.003	-0.022, 0.015	0.733	0.726, 0.780	0.754	6,743
Mothers outside of pregnancy							
Mental health							
Depression symptoms	OR	1.04	0.943, 1.148	0.398	0.507, 0.569	0.538	4,725
Anxiety symptoms	OR	0.98	0.890, 1.077	0.641	0.340, 0.401	0.370	4,740
Bulimia	OR	1.11	0.932, 1.309	0.225	0.180, 0.231	0.205	6,799
Drug addiction	OR	0.99	0.657, 1.481	0.943	0.941, 0.968	0.956	6,799
Alcoholism	OR	0.95	0.697, 1.287	0.706	0.697, 0.753	0.726	6,799
Schizophrenia	OR	0.43	0.244, 0.772	0.008	0.021, 0.044	0.031	6,799
Anorexia Nervosa	OR	1.08	0.899, 1.289	0.390	0.354, 0.415	0.384	6,799

Severe depression	OR	1.05	0.953, 1.166	0.277	0.218, 0.272	0.244	6,799
Other psychiatric problem	OR	1.05	0.867, 1.266	0.601	0.529, 0.591	0.560	6,799
Substance use							
Tobacco							
Ever smoking	OR	1.01	0.959, 1.064	0.679	0.626. 0.685	0.656	7,194
Number of cigarettes smoked past 2 weeks	Beta	0.30	-0.271, 0.879	0.300	0.270, 0.327	0.298	845
Number of cigarettes smoked before pregnancy	Beta	0.04	-0.028, 0.111	0.245	0.224, 0.279	0.251	3,426
Alcohol							
Alcohol drinking before pregnancy	OR	0.97	0.876, 1.078	0.558	0.016, 0.514	0.545	7,199
Binge drinking	Beta	0.004	-0.024, 0.032	0.786	0.752, 0.804	0.779	4,867
Daily alcohol units at child age 4	Beta	0.01	-0.013, 0.027	0.518	0.467, 0.529	0.498	5,680
Daily alcohol units at child age 8	Beta	0.01	-0.016, 0.044	0.347	0.354, 0.415	0.384	2,707
AUDIT score	Beta	0.01	-0.013, 0.028	0.473	0.450, 0.512	0.481	2,424
Non-mental health							
Life events	Beta	-0.03	-0.059, 0.008	0.141	0.115, 0.159	0.136	4,219
Sleep duration	Beta	-0.01	-0.034, 0.019	0.588	0.535, 0.597	0.588	1,867
Impulsivity personality trait	Beta	0.04	-0.063, 0.146	0.436	0.397, 0.459	0.428	4,847
Monotony avoidance personality trait	Beta	-0.11	-0.251, 0.037	0.144	0.131, 0.177	0.153	4,794
Anger personality trait	Beta	0.01	-0.115, 0.144	0.830	0.784, 0.834	0.810	4,769
Suspicion personality trait	Beta	-0.02	-0.128, 0.095	0.772	0.718, 0.773	0.746	4,856
Detachment personality trait	Beta	0.01	-0.102, 0.125	0.841	0.815, 0.861	0.839	4,753
Physical activity	OR	0.97	0.890, 1.050	0.387	0.015, 0.340	0.370	2,787
Social class	Beta	-0.01	-0.053, 0.035	0.696	0.680, 0.737	0.709	2,906
Education	Beta	0.002	-0.030, 0.035	0.889	0.882, 0.920	0.902	4,919
BMI before pregnancy	Beta	0.08	-0.008, 0.174	0.075	0.058, 0.091	0.073	6,398
Image perception before pregnancy	Beta	-0.003	-0.029, 0.023	0.820	0.796, 0.844	0.821	6,623

Note: OR-odds ratio; 95% CI – 95% confidence intervals

Appendix 4.5. Associations between offspring caffeine PRS and offspring outcomes in adolescence

		Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Offspring: Adolescence							
Mental health							
Conduct disorder symptoms	Beta	0.01	-0.014, 0.039	0.362	0.332, 0.393	0.362	3,834
Depression symptoms score age 18	Beta	0.01	-0.013, 0.039	0.314	0.288, 0.347	0.317	3,303
Specific phobia symptoms	Beta	0.001	-0.019, 0.020	0.937	0.935, 0.963	0.950	3,293
Emotional problems score	Beta	-0.02	-0.047, 0.002	0.072	0.063, 0.097	0.079	3,593
Anxiety symptoms	Beta	0.001	-0.024, 0.026	0.913	0.899, 0.934	0.918	3,293
Eating disorder age 13	Beta	-0.001	-0.003, 0.001	0.289	0.346, 0.407	0.376	4,256
Eating disorder age 16	Beta	0.003	-0.001, 0.007	0.184	0.166, 0.216	0.190	3,543
ADHD symptoms	Beta	-0.03	-0.065, 0.010	0.146	0.142, 0.188	0.164	3,435
Depression score age 14 (MFQ)	Beta	-0.002	-0.016, 0.013	0.835	0.817, 0.863	0.841	4,574
Depression score age 17 (MFQ)	Beta	-0.003	-0.015, 0.010	0.685	0.647, 0.706	0.677	3,212
Psychosis negative symptoms age 16	Beta	<0.001	-0.037, 0.036	0.996	0.993, 1.000	0.998	3,511
Total behavioural difficulties	Beta	-0.02	-0.056, 0.022	0.397	0.364, 0.425	0.394	3,603
Psychosis positive symptoms age 12	Beta	0.01	-0.006, 0.024	0.230	0.198, 0.250	0.223	4,974
Psychosis positive symptoms age 18	Beta	0.01	-0.006, 0.027	0.200	0.097, 0.137	0.116	3,403
PTSD disorder symptoms	Beta	-0.01	-0.027, 0.002	0.091	0.052, 0.084	0.067	4,008
Self-harming behaviour	OR	0.99	0.811, 1.196	0.869	0.836, 0.880	0.859	2,576
Oppositional-defiant disorder symptoms age 15	Beta	-0.01	-0.036, 0.013	0.367	0.561, 0.623	0.592	3,436
Substance use							
Tobacco							
Age when first smoked a cigarette	Beta	-0.01	-0.056, 0.030	0.553	0.535, 0.597	0.566	1,064
Has smoked a cigarette	OR	1.05	0.927, 1.179	0.443	0.384, 0.446	0.415	2,089
Total number of cigarettes smoked age 14	OR	0.99	0.767, 1.277	0.931	0.900, 0.935	0.919	461
Total number of cigarettes smoked age 18	Beta	0.07	-0.023, 0.162	0.142	0.114, 0.158	0.135	1,144
Alcohol							
Number of drinks to feel different	Beta	-0.04	-0.154, 0.076	0.505	0.494, 0.556	0.525	299

Binge drinking age 13	Beta	0.01	-0.094, 0.113	0.854	0.834, 0.878	0.857	464
Number of times had whole drink age 13	Beta	0.01	-0.059, 0.083	0.748	0.700, 0.756	0.729	1,103
Number of alcoholic drinks on a typical day	Beta	-0.01	-0.058, 0.034	0.609	0.580, 0.641	0.611	2,826
Binge drinking age 18	Beta	0.01	-0.036, 0.056	0.670	0.632, 0.691	0.662	2,829
Frequency having alcoholic drinks	Beta	0.01	-0.020, 0.042	0.485	0.462, 0.524	0.493	2,886
AUDIT risk score age 18	Beta	-0.01	-0.030, 0.017	0.562	0.539, 0.601	0.570	3,008
AUDIT total score age 18	Beta	0.01	-0.031, 0.050	0.647	0.986, 0.997	0.993	3,008
Number of drinks needed to feel tipsy	Beta	-0.02	-0.059, 0.029	0.500	0.461, 0.523	0.492	2,391
Other substances							
Cannabis use	OR	0.98	0.900, 1.060	0.551	0.494, 0.556	0.525	3,571
Frequency of cannabis use	Beta	0.02	-0.057, 0.093	0.636	0.613, 0.674	0.644	1,035
Non-mental health							
BMI	Beta	0.03	-0.100, 0.161	0.645	0.612, 0.673	0.643	3,606
Agreeableness personality trait	Beta	0.07	-0.080, 0.211	0.376	0.368, 0.430	0.399	4,279
Conscientiousness personality trait	Beta	-0.04	-0.218, 0.130	0.617	0.600, 0.661	0.631	4,162
Intellect personality trait	Beta	0.10	-0.069, 0.269	0.245	0.223, 0.278	0.250	4,263
Emotional stability personality trait	Beta	-0.07	-0.263, 0.130	0.506	0.472, 0.534	0.503	4,224
Extraversion personality trait	Beta	-0.04	-0.243, 0.159	0.682	0.657, 0.716	0.687	4,354
Frequency of doing exercise	Beta	-0.01	-0.032, 0.014	0.450	0.443, 0.505	0.474	4,270
Sleep duration (hours of sleep)	Beta	-0.02	-0.047, 0.014	0.294	0.260, 0.317	0.288	3,726
GCSE grades A-C	OR	1.47	1.146, 1.877	0.005	0.000, 0.004	<0.001	2,360
GCSE grades D-G	OR	1.01	0.914, 1.109	0.876	0.846, 0.889	0.869	2,182
IQ	Beta	0.14	-0.293, 0.569	0.531	0.497, 0.559	0.528	3,720
Sleep initiation	Beta	0.02	-0.019, 0.050	0.385	0.353, 0.414	0.383	3,626
Sleep maintenance	Beta	-0.003	-0.028, 0.022	0.804	0.813, 0.859	0.837	3,418
Life events	Beta	-0.01	-0.045, 0.031	0.733	0.690, 0.747	0.719	3,376

Note: OR-odds ratio; 95% CI – 95% confidence intervals

Appendix 4.6. Associations between maternal and offspring lifetime smoking PRSs and offspring phenotypes in childhood

		Maternal lifetime smoking PRS analyses						Offspring lifetime smoking PRS analyses					
		Regression analyses			Permutation testing			Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
IQ	Beta	-0.74	-1.202, -0.282	0.002	<0.001, 0.007	0.002	4,675	-0.93	-1.371, -0.488	$3.73x10^{-5}$	<0.001, 0.004	<0.001	5,290
Conduct disorder	Beta	0.03	0.007, 0.045	0.009	0.003, 0.014	0.007	5,012	0.03	0.010, 0.048	0.003	0.001, 0.009	0.003	5,326
BMI	Beta	0.06	0.007, 0.119	0.029	0.020, 0.043	0.030	5,032	0.03	-0.025, 0.076	0.316	0.282, 0.341	0.311	5,799
Total caffeine	Beta	0.02	-0.003, 0.045	0.079	0.063, 0.097	0.079	4,067	0.02	-0.007, 0.038	0.187	0.170, 0.220	0.194	4,589
Sleep initiation	OR	0.95	0.892, 1.012	0.104	0.064, 0.099	0.080	5,150	0.97	0.911, 1.029	0.273	0.203, 0.256	0.229	5,476
Behavioural difficulties	Beta	0.03	-0.005, 0.056	0.107	0.089, 0.129	0.108	5,133	0.05	0.016, 0.075	0.003	<0.001, 0.007	0.002	5,452
ADHD	Beta	0.02	-0.006, 0.052	0.117	0.098, 0.139	0.117	4,916	0.04	0.009, 0.065	0.009	0.006, 0.020	0.011	5,219
Specific phobia	OR	1.22	0.916, 1.631	0.156	0.179, 0.230	0.204	5,100	0.82	0.628, 1.083	0.150	0.169, 0.219	0.193	5,470
Anxiety	Beta	-0.01	-0.033, 0.009	0.256	0.229, 0.284	0.256	4,993	-0.01	-0.034, 0.007	0.189	0.150, 0.198	0.173	5,355
Sleep duration	Beta	-0.01	-0.036, 0.010	0.259	0.243, 0.299	0.270	5,127	0.002	-0.021, 0.024	0.878	0.851, 0.893	0.873	5,443
Sleep maintenance	OR	1.02	0.952, 1.090	0.559	0.503, 0.565	0.534	5,127	0.98	0.924, 1.048	0.594	0.556, 0.618	0.587	5,448
Autism	OR	1.10	0.768, 1.589	0.563	0.512, 0.574	0.543	5,975	1.26	0.838, 1.891	0.243	0.163, 0.213	0.187	6,156
ODD	Beta	0.01	-0.014, 0.026	0.574	0.557, 0.619	0.588	4,943	0.03	0.012, 0.051	0.002	<0.001, 0.004	<0.001	5,319
Emotional problems	Beta	-0.01	-0.025, 0.016	0.656	0.630, 0.689	0.660	5,139	-0.01	-0.031, 0.008	0.248	0.210, 0.264	0.236	5,459
Depression	Beta	-0.003	-0.023, 0.018	0.809	0.783, 0.833	0.809	4,885	0.01	-0.010, 0.030	0.323	0.300, 0.359	0.329	5,434
Handedness	OR	1.01	0.914, 1.114	0.846	0.790, 0.839	0.815	4,849	1.01	0.924, 1.096	0.876	0.866, 0.906	0.887	5,399
Life events	Beta	-0.002	-0.020, 0.017	0.853	0.838, 0.882	0.861	5,167	0.01	-0.004, 0.032	0.117	0.101, 0.143	0.121	5,493

Note: OR - odds ratio; 95% CI – 95% confidence intervals

Appendix 4.7. Associations between maternal lifetime smoking PRS and maternal outcomes during and outside of pregnancy

		Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Mothers during pregnancy							
Mental health							
Depression (18wks)	OR	1.08	0.997, 1.163	0.060	0.034, 0.061	0.046	6,734
Depression (32wks)	OR	1.08	0.999, 1.164	0.053	0.015, 0.036	0.024	6,751
Anxiety (18 wks)	OR	1.06	0.980, 1.155	0.127	0.087, 0.126	0.105	6,645
Hypersensitivity to interpersonal rejection	Beta	-0.30	-0.657, 0.065	0.108	0.097, 0.137	0.116	7,167
Feelings becoming a parent	Beta	-0.01	-0.034, 0.009	0.266	0.236, 0.291	0.263	7,165
Substance use							
Caffeine							
Total caffeine (18wks)	Beta	6.76	4.239, 9.280	<0.001	<0.001, 0.004	<0.001	7,220
Total caffeine (32wks)	Beta	5.33	2.776, 7.874	<0.001	<0.001, 0.004	<0.001	6,767
Alcohol							
Binge drinking (18wks)	Beta	0.02	0.005, 0.042	0.012	0.003, 0.016	0.008	7,171
Binge drinking (32wks)	Beta	0.02	0.001, 0.039	0.044	0.049, 0.080	0.063	5,324
Weekly alcohol units (32wks)	Beta	0.13	0.034, 0.233	0.009	0.008, 0.025	0.015	4,294
Other substances							
Cannabis use during pregnancy	OR	1.11	0.942, 1.299	0.197	0.175, 0.225	0.199	6,918
Hard drugs	OR	1.05	0.670, 1.653	0.809	0.779, 0.829	0.805	7,147
Non-mental health							
Education	Beta	-0.09	-0.122, -0.065	<0.001	<0.001, 0.004	<0.001	6,954
Social class	Beta	0.06	0.037, 0.091	<0.001	<0.001, 0.004	<0.001	5,854
Life events during pregnancy	Beta	0.02	-0.010, 0.045	0.214	0.196, 0.248	0.221	6,744
Image perception during pregnancy	Beta	0.12	0.023, 0.219	0.016	0.011, 0.028	0.018	6,699
Image perception change	Beta	0.004	-0.087, 0.095	0.931	0.906, 0.940	0.924	6,549
Activity level compared with other pregnant women	Beta	-0.001	-0.019, 0.017	0.911	0.892, 0.928	0.911	6,611
Physical activity	OR	1.00	0.946, 1.061	0.952	0.941, 0.968	0.956	6,767

Vomited first three months in pregnancy	OR	0.98	0.928, 1.033	0.412	0.373, 0.435	0.404	6,797
Sleep (18 wks)	Beta	0.01	-0.003, 0.032	0.108	0.089, 0.129	0.108	6,742
Sleep (32 wks)	Beta	0.03	0.016, 0.052	<0.001	<0.001, 0.004	<0.001	6,743
Mothers outside of pregnancy							
Mental health							
Depression symptoms	OR	1.01	0.913, 1.109	0.886	0.876, 0.915	0.897	4,725
Anxiety symptoms	OR	1.01	0.915, 1.105	0.904	0.880, 0.918	0.900	4,740
Bulimia	OR	1.14	0.964, 1.349	0.114	0.083, 0.121	0.101	6,799
Drug addiction	OR	0.98	0.596, 1.620	0.941	0.912, 0.945	0.930	6,799
Alcoholism	OR	1.27	0.968, 1.667	0.079	0.101, 0.143	0.121	6,799
Schizophrenia	OR	1.59	0.870, 2.889	0.120	0.197, 0.249	0.222	6,799
Anorexia Nervosa	OR	1.15	0.932, 1.419	0.174	0.096, 0.136	0.115	6,799
Severe depression	OR	1.16	1.049, 1.280	0.007	0.001, 0.010	0.004	6,799
Other psychiatric problem	OR	1.16	0.949, 1.408	0.134	0.079, 0.117	0.097	6,799
Substance use							
Alcohol							
Alcohol drinking before pregnancy	OR	1.01	0.910, 1.122	0.833	0.816, 0.862	0.840	7,199
Binge drinking	Beta	0.04	0.009, 0.068	0.010	<0.001, 0.004	<0.001	4,867
Daily alcohol units at child age 4	Beta	0.03	0.007, 0.049	0.008	0.006, 0.020	0.011	5,680
Daily alcohol units at child age 8	Beta	-0.01	-0.039, 0.021	0.559	0.564, 0.626	0.595	2,707
AUDIT score	Beta	0.01	-0.007, 0.035	0.181	0.174, 0.224	0.198	2,424
Caffeine							
Total caffeine consumption	Beta	8.70	5.083, 12.313	2.46×10^{-6}	<0.001, 0.004	<0.001	4,783
Non-mental health							
Life events	Beta	0.03	-0.009, 0.060	0.142	0.117, 0.161	0.138	4,219
Sleep duration	Beta	-0.02	-0.046, 0.009	0.183	0.163, 0.213	0.187	1,867
Impulsivity personality trait	Beta	0.11	0.006, 0.217	0.039	0.033, 0.060	0.045	4,847
Monotony avoidance personality trait	Beta	0.18	0.037, 0.332	0.014	0.008, 0.025	0.015	4,794
Anger personality trait	Beta	0.25	0.115, 0.377	2.34×10^{-4}	<0.001, 0.004	<0.001	4,769
Suspicion personality trait	Beta	0.16	0.057, 0.272	0.003	0.003, 0.016	0.008	4,856
Detachment personality trait	Beta	-0.06	-0.175, 0.054	0.301	0.258, 0.315	0.286	4,753
Physical activity	OR	1.00	0.915, 1.085	0.929	0.919, 0.950	0.936	2,787

Social class	Beta	0.03	-0.015, 0.072	0.204	0.185, 0.237	0.210	2,906
Education	Beta	-0.08	-0.115, -0.051	4.33×10^{-7}	<0.001, 0.004	<0.001	4,919
BMI before pregnancy	Beta	0.16	0.065, 0.254	0.001	0.001, 0.010	0.004	6,398
Image perception before pregnancy	Beta	0.03	0.002, 0.054	0.037	0.029, 0.054	0.040	6,623

Note: OR-odds ratio; 95% CI – 95% confidence intervals

Appendix 4.8. Associations between offspring lifetime smoking PRS and offspring outcomes in adolescence

		Regression analyses			Permutation testing		
Phenotype	**Effect estimate**	**Effect size**	**95% CI**	**P-value**	**95% CI**	**P-value**	**Sample size**
Offspring: Adolescence							
Mental health							
Conduct disorder symptoms	Beta	0.06	0.031, 0.082	<0.001	<0.001, 0.004	<0.001	3,834
Psychosis positive symptoms age 12	Beta	0.02	0.010, 0.018	0.001	<0.001, 0.004	<0.001	4,974
Depression symptoms age 17 (MFQ)	Beta	0.02	0.007, 0.036	0.002	<0.001, 0.006	0.001	3,212
Total behavioural difficulties	Beta	0.06	0.019, 0.091	0.003	0.001, 0.009	0.003	4,055
Psychosis positive symptoms age 18	Beta	0.02	0.004, 0.018	0.014	0.004, 0.017	0.009	3,403
ADHD symptoms	Beta	0.03	-0.003, 0.030	0.075	0.078, 0.116	0.096	3,852
Eating disorder age 16	Beta	0.003	-0.001, 0.041	0.146	0.138, 0.184	0.160	3,543
Depression symptoms score age 17	Beta	0.02	-0.010, 0.039	0.228	0.218, 0.272	0.244	3,303
Specific phobia symptoms	Beta	0.01	-0.009, 0.031	0.301	0.261, 0.318	0.289	3,293
PTSD symptoms	Beta	0.01	-0.007, 0.027	0.360	0.340, 0.401	0.370	4,008
Oppositional defiant disorder	Beta	0.01	-0.013, 0.169	0.374	0.342, 0.403	0.372	3,436
Anxiety symptoms score	Beta	0.01	-0.015, 0.066	0.387	0.345, 0.406	0.375	3,293
Eating disorder age 13	Beta	0.001	-0.001, 0.007	0.475	0.454, 0.516	0.485	4,256
Depression symptoms age 14 (MFQ)	Beta	0.004	-0.010, 0.019	0.573	0.568, 0.630	0.599	4,574
Emotional problems symptoms	Beta	0.004	-0.018, 0.036	0.700	0.655, 0.714	0.685	4,073
Psychosis negative symptoms age 16	Beta	0.002	-0.034, 0.038	0.922	0.892, 0.928	0.911	3,511
Self-harming behaviour	OR	0.99	0.834, 1.185	0.944	0.927, 0.957	0.943	2,576
Substance use							
Alcohol							
Number of drinks needed to feel different	Beta	0.10	-0.020, 0.218	0.103	0.101, 0.143	0.121	299
Binge drinking age 13	Beta	0.09	-0.017, 0.197	0.099	0.073, 0.109	0.090	464
Number of times had a whole drink past 6 months	Beta	-0.01	-0.076, 0.062	0.840	0.825, 0.871	0.849	1,103
Number of alcoholic drinks on a typical day	Beta	0.04	-0.005, 0.082	0.083	0.058, 0.091	0.073	2,826
Binge drinking age 18	Beta	0.06	0.017, 0.109	0.007	0.002, 0.012	0.005	2,829

Frequency of having alcoholic drinks	Beta	-0.002	-0.032, 0.027	0.876	0.833, 0.877	0.856	2,886
AUDIT risk score age 18	Beta	0.04	0.014, 0.061	0.002	<0.001, 0.006	0.001	3,008
AUDIT total score age 18	Beta	0.04	-0.004, 0.075	0.082	0.088, 0.127	0.106	3,008
Number of drinks needed to feel tipsy	Beta	0.05	0.004, 0.089	0.032	0.030, 0.055	0.041	2,391
Tobacco							
Cannabis use	OR	1.07	0.990, 1.164	0.082	0.040, 0.069	0.053	3,571
Frequency of cannabis use	Beta	0.04	-0.031, 0.115	0.261	0.248, 0.305	0.276	1,035
Caffeine							
Total caffeine consumption	Beta	0.02	-0.019, 0.055	0.348	0.342, 0.403	0.372	3,405
Non-mental health							
Extraversion personality trait	Beta	0.45	0.244, 0.646	<0.001	<0.001, 0.004	<0.001	4,354
Conscientiousness personality trait	Beta	-0.19	-0.367, -0.008	0.041	0.030, 0.056	0.042	4,162
Agreeableness personality trait	Beta	0.01	-0.132, 0.151	0.893	0.896, 0.932	0.915	4,279
Intellect personality trait	Beta	-0.01	-0.174, 0.156	0.918	0.900, 0.935	0.919	4,263
Emotional stability personality trait	Beta	-0.07	-0.253, 0.124	0.501	0.489, 0.551	0.520	4,224
IQ	Beta	-0.74	-1.163, -0.320	0.001	<0.001, 0.004	<0.001	3,720
BMI	Beta	0.21	0.078, 0.331	0.001	0.001, 0.010	0.004	3,606
Sleep maintenance	Beta	0.03	0.008, 0.059	0.011	0.005, 0.018	0.010	3,418
GCSE grades D-G	OR	1.11	1.008, 1.213	0.036	0.011, 0.028	0.018	2,182
Frequency of doing exercise	Beta	-0.03	-0.048, -0.001	0.039	0.032, 0.059	0.044	4,270
Sleep duration (hours of sleep)	Beta	-0.03	-0.055, 0.005	0.097	0.088, 0.127	0.106	3,726
Sleep initiation (time to fall asleep)	Beta	0.03	-0.009, 0.060	0.150	0.127, 0.173	0.149	3,626
GCSE grades A-C	OR	0.84	0.652, 1.082	0.160	0.101, 0.142	0.120	2,360
Life events	Beta	0.01	-0.026, 0.047	0.570	0.583, 0.644	0.614	3,376

Note: OR-odds ratio; 95% CI – 95% confidence intervals

Appendix 4.9. Correlation between maternal smoking, caffeine and alcohol PRSs

	Smoking initiation PRS	**Lifetime smoking PRS**	**Caffeine PRS**	**Alcohol PRS**
Smoking initiation PRS	-	0.35	0.01	0.08
	Lifetime smoking PRS	-	-0.01	0.02
		Caffeine PRS	-	0.12

Appendix 5.1. Associations between maternal prenatal smoking and high risk of maternal reported offspring ADHD symptoms in MoBa (adjusted for maternal ADHD)

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (RS-DBD)	41,515	5,509			<0.001	28,507	3,655			<0.001	23,491	2,954			0.026
No cigarettes (ref)	39,162	4,993	-	-		27,093	3,360	-	-		22,430	2,748	-	-	
1-4 cigarettes	1260	234	1.56	1.350,1.805		764	138	1.19	0.969,1.450		572	94	1.04	0.813,1.318	
5-9 cigarettes	650	158	2.20	1.830,2.640		371	91	1.64	1.266,2.121		285	64	1.46	1.071,1.994	
>10 cigarettes	443	124	2.66	2.159,3.277		279	66	1.32	0.961,1.799		204	48	1.28	0.875,1.861	
Hyperactive	41,508	5,436			<0.001	28,504	3,600			<0.001	23,489	2,933			0.010
No cigarettes (ref)	39,158	4,916	-	-		27,092	3,308	-	-		22,429	2,719	-	-	
1-4 cigarettes	1,259	239	1.63	1.414,1.883		763	136	1.19	0.974,1.448		572	99	1.10	0.873,1.394	
5-9 cigarettes	649	159	2.26	1.884,2.712		371	90	1.63	1.263,2.094		285	64	1.43	1.055,1.939	
>10 cigarettes	442	122	2.66	2.152,3.278		278	66	1.34	0.982,1.836		203	51	1.36	0.938,1.970	
Inattentive	41,524	4,824			<0.001	28,512	3,186			0.030	23,494	2,571			0.195
No cigarettes (ref)	39,170	4,402	-	-		27,098	2,940	-	-		22,433	2,398	-	-	
1-4 cigarettes	1,261	198	1.47	1.259,1.719		764	119	1.14	0.924,1.416		572	81	1.00	0.776,1.299	
5-9 cigarettes	650	131	1.99	1.640,2.423		371	80	1.61	1.234,2.112		285	55	1.41	1.015,1.947	
>10 cigarettes	443	93	2.10	1.663,2.648		279	47	1.00	0.698,1.427		204	37	1.08	0.711,1.631	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals;*adjusted for child's gender, birth year, parity, maternal age, education, marital status, financial difficulties, depression, anxiety and ADHD symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partner's smoking*

Appendix 5.2. Associations between maternal smoking before pregnancy and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (RS-DBD)	41,263	5,471			<0.001	36,636	4,750			<0.001	30,013	3,807			0.051
No cigarettes (ref)	31,691	3,880	-	-		28,375	3,417	-	-		23,448	2,788	-	-	
1-4 cigarettes	4,364	574	1.09	0.988,1.193		3,837	497	0.97	0.871,1.075		3,117	395	0.94	0.830,1.054	
5-9 cigarettes	1,619	258	1.36	1.184,1.560		1,395	217	1.09	0.927,1.269		1,095	161	0.99	0.819,1.187	
>10 cigarettes	3,589	759	1.92	1.762,2.098		3,029	619	1.32	1.184,1.470		2,353	463	1.18	1.036,1.350	
Hyperactive	41,254	5,390			<0.001	36,626	4,693			<0.001	30,007	3,792			<0.001
No cigarettes (ref)	31,686	3,787	-	-		28,369	3,343	-	-		23,445	2,730	-	--	
1-4 cigarettes	4,364	597	1.17	1.064,1.282		3,837	523	1.06	0.958,1.179		3,117	427	1.07	0.952,1.203	
5-9 cigarettes	1,617	261	1.42	1.236,1.627		1,393	213	1.10	0.941,1.289		1,094	164	1.06	0.879,1.271	
>10 cigarettes	3,587	745	1.93	1.769,2.109		3,027	614	1.37	1.227,1.521		2,351	471	1.28	1.122,1.457	
Inattentive	41,271	4,791			<0.001	36,642	4,169			0.002	30,015	3,331			0.112
No cigarettes (ref)	31,694	3,432	-	-		28,375	3,022	-	-		23,446	2,464	-	-	
1-4 cigarettes	4,364	485	1.03	0.930,1.140		3,838	422	0.92	0.824,1.032		3,118	328	0.89	0.778,1.007	
5-9 cigarettes	1,620	230	1.36	1.181,1.573		1,396	193	1.08	0.917,1.274		1,095	141	1.00	0.825,1.218	
>10 cigarettes	3,593	644	1.80	1.638,1.974		3,033	532	1.24	1.101,1.387		2,356	398	1.17	1.012,1.341	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals;*adjusted for child's gender, birth year, parity, maternal age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partner's smoking before partner's pregnancy*

Appendix 5.3. Associations between maternal and paternal prenatal smoking and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
Maternal															
ADHD (DAWBA)	5,767	808			<0.001	4,584	576			0.087	3,452	396			0.331
No cigarettes (ref)	4,433	530	-	-		3,648	404	-	-		2,792	286	-	-	
1-4 cigarettes	296	63	1.99	1.486,2.668		226	46	1.67	1.157,2.404		164	30	1.63	1.041,2.554	
5-9 cigarettes	314	47	1.30	0.938,1.791		230	31	0.92	0.604,1.405		163	20	0.82	0.481,1.396	
>10 cigarettes	724	168	2.23	1.831,2.704		480	95	1.32	0.984,1.762		333	60	1.24	0.863,1.782	
Hyperactive	5,766	726			<0.001	4,584	520			0.253	3,452	357			0.419
No cigarettes (ref)	4,432	489	-	-		3,648	372	-	-		2,792	263	-	-	
1-4 cigarettes	296	57	1.92	1.419,2.606		226	42	1.68	1.155,2.451		164	28	1.76	1.110,2.795	
5-9 cigarettes	314	44	1.31	0.943,1.832		230	32	1.17	0.769,1.777		163	22	1.26	0.748,2.107	
>10 cigarettes	724	136	1.87	1.514,2.298		480	74	1.15	0.836,1.567		333	44	1.10	0.736,1.639	
Inattentive	5,767	713			<0.001	4,583	508			0.503	3,450	358			0.822
No cigarettes (ref)	4,433	476	-	-		3,648	365	-	-		2,791	266	-	-	
1-4 cigarettes	297	53	1.81	1.322,2.467		226	41	1.60	1.094,2.337		164	26	1.40	0.875,2.236	
5-9 cigarettes	313	39	1.18	0.835,1.677		229	23	0.73	0.454,1.165		162	14	0.59	0.322,1.080	
>10 cigarettes	724	145	2.08	1.695,2.556		480	79	1.17	0.859,1.591		333	52	1.13	0.777,1.656	
ADHD (SDQ)	5,764	633			<0.001	4,587	444			0.025	3,455				0.102
No cigarettes (ref)	4,430	405	-	-		3,650	303	-	-		2,795	217	-	-	
1-4 cigarettes	296	46	1.83	1.314,2.545		226	34	1.56	1.034,2.345		164	24	1.65	1.009,2.682	
5-9 cigarettes	314	40	1.45	1.025,2.053		230	27	1.08	0.687,1.689		162	21	1.29	0.756,2.185	
>10 cigarettes	724	142	2.43	1.966,2.991		481	80	1.45	1.055,1.981		334	49	1.34	0.903,1.985	

Paternal															
ADHD (DAWBA)	4,081	509			<0.001	3,075	334			0.173	3,067	332			0.454
No cigarettes (ref)	2,648	287	-	-		2,100	200	-	-		2,097	200	-	-	
1-4 cigarettes	218	26	1.11	0.726,1.708		162	18	1.07	0.633,1.822		161	18	1.04	0.608,1.769	
5-9 cigarettes	186	24	1.22	0.780,1.903		132	15	0.98	0.547,1.753		132	15	0.96	0.535,1.734	
>10 cigarettes	1,029	172	1.65	1.346,2.026		681	101	1.24	0.926,1.653		677	99	1.14	0.834,1.545	
Hyperactive	4,081	462			0.004	3,075	313			0.802	3,067	310			0.413
No cigarettes (ref)	2,648	276	-	-		2,100	203	-	-		2,097	202	-	-	
1-4 cigarettes	218	24	1.06	0.683,1.654		162	17	1.03	0.601,1.777		161	17	0.99	0.573,1.716	
5-9 cigarettes	186	18	0.92	0.557,1.521		132	11	0.70	0.361,1.344		132	11	0.67	0.346,1.296	
>10 cigarettes	1,029	144	1.40	1.127,1.735		681	82	0.99	0.727,1.349		677	80	0.90	0.646,1.248	
Inattentive	4,079	456			<0.001	3,073	307			0.196	3,065	306			0.215
No cigarettes (ref)	2,647	250	-	-		2,099	178	-	-		2,096	178	-	-	
1-4 cigarettes	218	31	1.59	1.064,2.375		162	23	1.63	1.005,2.643		161	23	1.63	0.999,2.652	
5-9 cigarettes	186	20	1.16	0.713,1.870		132	13	0.94	0.507,1.729		132	13	0.96	0.519,1.790	
>10 cigarettes	1,028	155	1.70	1.373,2.110		680	93	1.23	0.914,1.664		676	92	1.23	0.900,1.694	
ADHD (SDQ)	4,079	401			<0.001	3,079				0.124	3,071	258			0.782
No cigarettes (ref)	2,645	219	-	-		2,101	151	-	-		2,098	151	-	-	
1-4 cigarettes	218	25	1.44	0.925,2.226		162	18	1.45	0.847,2.478		161	18	1.39	0.805,2.384	
5-9 cigarettes	186	16	1.04	0.613,1.773		132	9	0.76	0.369,1.559		132	9	0.69	0.334,1.440	
>10 cigarettes	1,030	141	1.76	1.403,2.201		684	83	1.32	0.961,1.817		680	80	1.08	0.766,1.520	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partners' prenatal smoking*

Appendix 5.4. Associations between maternal smoking before pregnancy and high risk of maternal and teacher reported offspring ADHD symptoms in GenR

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (CPRS-R)	3,028	444			0.001	1,979	277			0.100	1,481	194			0.080
No cigarettes (ref)	1,883	248	-	-		1,226	159	-	-		928	110	-	-	
1-4 cigarettes	427	66	1.21	0.898,1.618		269	37	1.02	0.681,1.518		203	29	1.18	0.737,1.881	
5-9 cigarettes	250	40	1.26	0.873,1.806		161	22	0.95	0.575,1.578		112	14	0.94	0.489,1.787	
>10 cigarettes	468	90	1.57	1.203,2.048		323	59	1.41	0.977,2.031		238	41	1.60	1.007,2.527	
Hyperactive	3,031	336			0.004	1,983	194			0.059	1,482	138			0.111
No cigarettes (ref)	1,888	187	-	-		1,231	105	-	-		930	72	-	-	
1-4 cigarettes	426	53	1.29	0.934,1.789		269	33	1.53	0.993,2.366		203	24	1.44	0.858,2.431	
5-9 cigarettes	250	26	1.06	0.685,1.628		161	15	1.04	0.575,1.883		112	10	0.93	0.442,1.961	
>10 cigarettes	467	70	1.60	1.193,2.155		322	41	1.48	0.964,2.272		237	32	1.62	0.958,2.738	
Inattentive	3,030	380			0.079	1,985	231			0.715	1,484	165			0.192
No cigarettes (ref)	1,887	224	-	-		1,232	142	-	-		931	99	-	-	
1-4 cigarettes	426	54	1.08	0.784,1.481		269	27	0.82	0.521,1.275		203	21	0.93	0.553,1.569	
5-9 cigarettes	250	32	1.09	0.733,1.620		161	17	0.84	0.483,1.460		112	12	0.97	0.493,1.923	
>10 cigarettes	467	70	1.31	0.980,1.749		323	45	1.15	0.771,1.711		238	33	1.46	0.892,2.387	
ADHD (CBCL)	4,076	596			<0.001	2,484	332			0.006	1,778	214			0.083
No cigarettes (ref)	2,477	315	-	-		1,497	167	-	-		1,090	111	-	-	
1-4 cigarettes	570	75	1.04	0.794,1.362		341	43	1.09	0.749,1.581		240	25	0.93	0.571,1.499	
5-9 cigarettes	357	70	1.67	1.257,2.230		212	39	1.58	1.056,2.372		144	25	1.46	0.870,2.434	
>10 cigarettes	672	136	1.74	1.394,2.175		434	83	1.45	1.051,2.013		304	53	1.40	0.912,2.139	
ADHD (TRF)	2,997	464			<0.001	1,633	213			0.002	1,119	123			0.019
No cigarettes (ref)	1,791	252	-	-		970	108	-	-		675	65	-	-	
1-4 cigarettes	402	52	0.91	0.659,1.250		212	22	1.00	0.594,1.666		144	9	0.58	0.268,1.257	
5-9 cigarettes	282	57	1.55	1.124,2.130		156	25	1.53	0.910,2.586		98	13	1.46	0.722,2.968	
>10 cigarettes	522	103	1.50	1.165,1.934		295	58	1.86	1.232,2.791		202	36	1.95	1.111,3.422	

*Note: CPRS-R – Revised Conners' Parent Rating Scale; CBCL – Child Behavior Checklist; TRF – Teacher Report Form; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, parity, maternal ethnicity, age, education, anxiety and depression symptoms, financial difficulties, alcohol use before pregnancy and prenatal caffeine consumption; **additionally adjusted for partner's smoking before pregnancy*

Appendix 5.5. Associations between maternal and paternal prenatal smoking and high risk of maternal reported offspring ADHD symptoms in ALSPAC (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (DAWBA)	5,201	709			<0.001			0.130			0.654
No cigarettes (ref)	4,319	542	-	-		-	-		-	-	
1-4 cigarettes	244	38	1.29	0.899,1.838		0.96	0.663,1.400		0.84	0.576,1.232	
5-9 cigarettes	228	44	1.67	1.185,2.344		1.22	0.846,1.767		1.07	0.734,1.553	
>10 cigarettes	410	85	1.82	1.412,2.352		1.23	0.916,1.637		1.07	0.797,1.449	
Hyperactive	5,211	622			<0.001			0.669			0.839
No cigarettes (ref)	4,329	486	-	-		-	-		-	-	
1-4 cigarettes	245	32	1.19	0.810,1.743		0.91	0.615,1.360		0.84	0.559,1.254	
5-9 cigarettes	227	35	1.44	0.993,2.092		1.05	0.704,1.555		0.98	0.652,1.463	
>10 cigarettes	410	69	1.60	1.215,2.107		1.08	0.790,1.465		0.98	0.715,1.348	
Inattentive	5,208	686			<0.001			0.246			0.651
No cigarettes (ref)	4,326	541	-	-		-	-		-	-	
1-4 cigarettes	243	31	1.02	0.694,1.507		0.80	0.538,1.199		0.73	0.487,1.099	
5-9 cigarettes	228	39	1.44	1.011,2.062		1.16	0.792,1.702		1.06	0.721,1.568	
>10 cigarettes	411	75	1.56	1.197,2.038		1.20	0.889,1.622		1.09	0.802,1.488	
ADHD (SDQ)	5,405	561			<0.001			0.030			0.159
No cigarettes (ref)	4,459	415	-	-		-	-		-	-	
1-4 cigarettes	249	35	1.59	1.099,2.310		1.29	0.880,1.892		1.17	0.792,1.732	
5-9 cigarettes	238	28	1.30	0.865,1.952		0.95	0.619,1.461		0.88	0.568,1.358	
>10 cigarettes	459	83	2.15	1.661,2.785		1.43	1.068,1.918		1.30	0.963,1.764	

Paternal										
ADHD (DAWBA)	4,647	618			<0.001			0.001		0.005
No cigarettes (ref)	3,284	381	-	-		-	-		-	-
1-4 cigarettes	235	34	1.29	0.882,1.882		1.19	0.804,1.758		1.18	0.799,1.755
5-9 cigarettes	184	28	1.37	0.902,2.074		1.25	0.816,1.930		1.24	0.803,1.912
>10 cigarettes	944	175	1.73	1.426,2.109		1.44	1.155,1.784		1.38	1.097,1.730
Hyperactive	4,656	532			<0.001			0.045		0.105
No cigarettes (ref)	3,291	340	-	-		-	-		-	-
1-4 cigarettes	235	28	1.17	0.779,1.770		1.12	0.737,1.711		1.11	0.728,1.700
5-9 cigarettes	183	16	0.83	0.492,1.406		0.74	0.431,1.263		0.73	0.424,1.248
>10 cigarettes	947	148	1.61	1.305,1.980		1.31	1.040,1.648		1.26	0.991,1.606
Inattentive	4,656	610			<0.001			0.076		0.089
No cigarettes (ref)	3,289	393	-	-		-	-		-	-
1-4 cigarettes	237	36	1.32	0.912,1.911		1.21	0.828,1.780		1.24	0.841,1.817
5-9 cigarettes	184	26	1.21	0.790,1.860		1.11	0.715,1.729		1.13	0.723,1.760
>10 cigarettes	946	155	1.44	1.180,1.767		1.22	0.976,1.525		1.22	0.966,1.538
ADHD (SDQ)	4,793				<0.001			0.001		0.023
No cigarettes (ref)	3,353	289	-	-		-	-		-	-
1-4 cigarettes	239	29	1.46	0.975,2.199		1.38	0.909,2.091		1.32	0.869,2.013
5-9 cigarettes	195	23	1.42	0.903,2.227		1.27	0.802,2.022		1.22	0.762,1.937
>10 cigarettes	1,006	144	1.77	1.430,2.193		1.4	1.163,1.857		1.33	1.036,1.699

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partners' prenatal smoking*

Appendix 5.6. Associations between maternal and paternal prenatal smoking and high risk of maternal reported offspring ADHD symptoms in GenR (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (CPRS-R)	1,535	196			0.004			0.013			0.018
No cigarettes (ref)	1,219	145	-	-		-	-		-	-	
1-4 cigarettes	165	21	1.08	0.662,1.762		1.00	0.600,1.665		1.01	0.592,1.720	
5-9 cigarettes	82	13	1.40	0.753,2.588		1.29	0.669,2.476		1.26	0.639,2.484	
>10 cigarettes	69	17	2.42	1.363,4.301		2.43	1.301,4.520		2.48	1.293,4.755	
Hyperactive	1,536	143			0.017			0.034			0.217
No cigarettes (ref)	1,221	107	-	-		-	-		-	-	
1-4 cigarettes	165	14	0.97	0.539,1.728		0.99	0.540,1.798		0.77	0.413,1.440	
5-9 cigarettes	81	9	1.30	0.633,2.676		1.21	0.564,2.572		0.97	0.445,2.123	
>10 cigarettes	69	13	2.42	1.281,4.562		2.5	1.230,4.913		1.99	0.964,4.099	
Inattentive	1,537	170			0.125			0.244			0.143
No cigarettes (ref)	1,221	133	-	-		-	-		-	-	
1-4 cigarettes	165	15	0.82	0.467,1.433		0.76	0.425,1.349		0.81	0.442,1.470	
5-9 cigarettes	82	7	0.76	0.345,1.691		0.68	0.299,1.552		0.68	0.292,1.589	
>10 cigarettes	69	15	2.27	1.247,4.139		2.20	1.150,4.206		2.49	1.259,4.932	
ADHD (CBCL)	1,835	211			<0.001			<0.001			0.031
No cigarettes (ref)	1,432	140	-	-		-	-		-	-	
1-4 cigarettes	211	31	1.59	1.045,2.417		1.53	0.983,2.375		1.22	0.770,1.942	
5-9 cigarettes	107	21	2.25	1.356,3.745		1.94	1.119,3.374		1.53	0.863,2.725	
>10 cigarettes	85	19	2.66	1.549,4.556		2.26	1.255,4.061		1.80	0.972,3.323	
ADHD (TRF)	1,148	125			0.002			0.017			0.059
No cigarettes (ref)	878	85	-	-		-	-		-	-	
1-4 cigarettes	141	16	1.19	0.678,2.104		1.25	0.681,2.293		1.01	0.529,1.908	
5-9 cigarettes	75	12	1.78	0.922,3.427		1.91	0.907,4.006		1.59	0.737,3.449	
>10 cigarettes	54	12	2.67	1.351,5.258		2.36	1.064,5.224		2.16	0.944,4.918	

Paternal										
ADHD (CPRS-R)	1,930	260			0.316			0.605		0.237
No cigarettes (ref)	1,148	149	-	-		-	-	-	-	
1-4 cigarettes	328	43	1.01	0.703,1.456		0.90	0.619,1.320	0.89	0.606,1.310	
5-9 cigarettes	132	20	1.20	0.722,1.986		0.93	0.546,1.583	0.87	0.502,1.518	
>10 cigarettes	322	48	1.18	0.826,1.670		0.91	0.625,1.332	0.79	0.522,1.180	
Hyperactive	1,930	186			0.013			0.330		0.448
No cigarettes (ref)	1,148	98	-	-		-	-	-	-	
1-4 cigarettes	327	31	1.12	0.734,1.715		1.04	0.669,1.617	1.09	0.695,1.704	
5-9 cigarettes	132	15	1.37	0.772,2.444		1.05	0.570,1.929	1.12	0.598,2.106	
>10 cigarettes	323	42	1.60	1.090,2.353		1.24	0.820,1.886	1.18	0.757,1.852	
Inattentive	1,931	233			0.843			0.082		0.078
No cigarettes (ref)	1,149	139	-	-		-	-	-	-	
1-4 cigarettes	327	40	1.01	0.696,1.474		0.92	0.621,1.355	0.94	0.633,1.401	
5-9 cigarettes	132	17	1.07	0.626,1.824		0.84	0.478,1.483	0.91	0.506,1.621	
>10 cigarettes	323	37	0.94	0.639,1.382		0.69	0.458,1.049	0.66	0.423,1.024	
ADHD (CBCL)	2,323	275			<0.001			0.003		0.039
No cigarettes (ref)	1,361	130	-	-		-	-	-	-	
1-4 cigarettes	381	49	1.40	0.985,1.984		1.35	0.936,1.943	1.32	0.914,1.919	
5-9 cigarettes	164	25	1.70	1.072,2.705		1.44	0.884,2.333	1.33	0.807,2.195	
>10 cigarettes	417	71	1.94	1.421,2.657		1.64	1.167,2.293	1.46	1.011,2.093	
ADHD (TRF)	1,445	151			0.005			0.211		0.347
No cigarettes (ref)	816	68	-	-		-	-	-	-	
1-4 cigarettes	242	29	1.50	0.945,2.374		1.35	0.817,2.220	1.41	0.851,2.344	
5-9 cigarettes	109	17	2.03	1.145,3.608		1.45	0.781,2.695	1.52	0.806,2.876	
>10 cigarettes	278	37	1.69	1.103,2.585		1.30	0.814,2.081	1.21	0.732,2.002	

*Note: CPRS-R – Revised Conners' Parent Rating Scale; CBCL – Child Behavior Checklist; TRF – Teacher Report Form; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, parity, parental ethnicity, age, education, anxiety and depression symptoms, financial difficulties and parental smoking and prenatal caffeine consumption in the maternal model; **additionally adjusted for partner's smoking*

Appendix 5.7. Associations between maternal and paternal prenatal smoking and high risk of maternal reported offspring ADHD symptoms in MoBa (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (RS-DBD)	28,055	3,543			<0.001			0.001			0.006
No cigarettes (ref)	26,706	3,280	-	-		-	-		-	-	
1-4 cigarettes	707	111	1.33	1.082,1.635		0.98	0.788,1.219		0.95	0.761,1.182	
5-9 cigarettes	383	87	2.10	1.645,2.679		1.56	1.201,2.038		1.49	1.136,1.941	
>10 cigarettes	259	65	2.39	1.810,3.163		1.47	1.078,2.008		1.38	1.000,1.893	
Hyperactive	28,051	3,507			<0.001			<0.001			<0.001
No cigarettes (ref)	26,704	3,232	-	-		-	-		-	-	
1-4 cigarettes	707	117	1.44	1.177,1.763		1.08	0.871,1.329		1.04	0.840,1.286	
5-9 cigarettes	382	91	2.27	1.789,2.884		1.68	1.300,2.170		1.60	1.228,2.073	
>10 cigarettes	258	67	2.55	1.924,3.373		1.57	1.152,2.127		1.45	1.061,1.991	
Inattentive	28,058	3,102			<0.001			0.014			0.041
No cigarettes (ref)	26,708	2,877	-	-		-	-		-	-	
1-4 cigarettes	708	101	1.38	1.110,1.711		1.01	0.800,1.265		0.99	0.783,1.243	
5-9 cigarettes	383	70	1.85	1.423,2.412		1.37	1.032,1.815		1.32	0.996,1.760	
>10 cigarettes	259	54	2.18	1.615,2.947		1.36	0.977,1.902		1.31	0.929,1.837	

					Paternal					
ADHD (RS-DBD)	10,738	1,454			0.002			0.142		0.417
No cigarettes (ref)	8,965	1,193	-	-		-	-	-	-	
1-4 cigarettes	998	120	0.89	0.729,1.088		0.85	0.690,1.035	0.83	0.680,1.021	
5-9 cigarettes	211	40	1.52	1.074,2.162		1.38	0.960,1.969	1.32	0.919,1.889	
>10 cigarettes	564	101	1.42	1.136,1.777		1.19	0.933,1.511	1.09	0.846,1.404	
Hyperactive	10,736	1,424			0.001			0.075		0.242
No cigarettes (ref)	8,964	1,157	-	-		-	-	-	-	
1-4 cigarettes	997	132	1.03	0.849,1.249		0.99	0.809,1.201	0.98	0.801,1.190	
5-9 cigarettes	211	39	1.53	1.075,2.178		1.39	0.967,1.995	1.35	0.939,1.945	
>10 cigarettes	564	96	1.38	1.100,1.742		1.16	0.909,1.485	1.09	0.843,1.411	
Inattentive	10,740	1,248			0.002			0.117		0.295
No cigarettes (ref)	8,966	1,018	-	-		-	-	-	-	
1-4 cigarettes	998	110	0.97	0.785,1.191		0.91	0.734,1.123	0.90	0.727,1.115	
5-9 cigarettes	211	31	1.35	0.913,1.980		1.19	0.803,1.767	1.16	0.784,1.725	
>10 cigarettes	565	89	1.46	1.154,1.847		1.22	0.948,1.579	1.16	0.887,1.509	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals;*adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal alcohol and caffeine consumption; **additionally adjusted for partner's smoking*

Appendix 5.8. Associations between maternal unweighted PRSs and maternal exposure phenotypes in ALSPAC

Exposure	Beta	95% CI	P-value	Sample size
Smoking heaviness	0.02	0.008, 0.023	<0.001	1,537
Lifetime smoking*	0.01	0.007, 0.124	<0.001	7,107
Lifetime smoking**	1.03	1.022, 1.044	<0.001	3,413
Alcohol consumption	0.004	0.002, 0.007	<0.001	3,962
Coffee consumption	3.49	1.477, 5.511	<0.001	7,074

*Note: *smoking heaviness phenotype; **smoking cessation phenotype (in OR's); 95% CI – 95% confidence intervals; adjusted for principal components*

Appendix 5.9. Associations between maternal unweighted PRSs and maternal exposure phenotypes in MoBa

Exposure	Beta	95% CI	P-value	Sample size
Smoking heaviness	0.01	0.002, 0.180	0.021	1,029
Lifetime smoking*	0.004	0.003, 0.005	<0.001	14,488
Lifetime smoking**	1.02	1.005, 1.027	0.004	3,118
Alcohol consumption	0.001	-0.016, 0.018	0.911	1,362
Alcohol consumption***	1.06	0.258, 1.859	0.010	12,953
Coffee consumption	1.14	0.279, 2.008	0.010	14,583

*Note: *smoking heaviness phenotype; **smoking cessation phenotype (in OR's); 95% CI – 95% confidence intervals; ***alcohol consumption before pregnancy; adjusted for principal components, birth year and genotyping batch*

Appendix 5.10. Associations between maternal smoking heaviness PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	2.51	0.816, 7.735	0.108	2.40	0.764, 7.510	0.134	833
Hyperactive	2.30	0.736, 7.180	0.152	2.19	0.688, 6.947	0.185	833
Inattentive	3.00	0.888, 10.122	0.077	2.68	0.781, 9.198	0.117	833
ADHD (SDQ)	1.38	0.419, 4.560	0.595	1.31	0.390, 4.364	0.666	834

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Appendix 5.11. Associations between maternal lifetime smoking PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	2.68	1.025, 7.022	0.044	2.70	1.026, 7.079	0.044	3,486
Hyperactive	2.39	0.883, 6.478	0.086	2.43	0.893, 6.603	0.082	3,485
Inattentive	1.91	0.685, 5.321	0.216	1.91	0.682, 5.332	0.219	3,487
ADHD (SDQ)	2.97	1.029, 8.548	0.044	3.00	1.034, 8.688	0.043	3,486

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Appendix 5.12. Associations between maternal prenatal alcohol consumption and high risk of maternal reported offspring ADHD symptoms in MoBa (adjusted for maternal ADHD)

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD RS-DBD)	38,134	5,030			<0.001	28,507	3,655			<0.001	9,031	1,187			0.001
None (ref)	33,605	4,342	-	-		25,110	3,140	-	-		8,317	1,059	-	-	
<1 unit a week	4,366	663	1.21	1.104,1.319		3,271	500	1.33	1.197,1.488		691	126	1.53	1.238,1.891	
>1 unit a week	163	25	1.22	0.795,1.875		126	15	0.85	0.476,1.516		NA	NA	NA	NA	
Hyperactive	38,127	4,957			<0.001	28,504	3,600			<0.001	9,030	1,149			0.007
None (ref)	33,601	4,281	-	-		25,109	3,097	-	-		8,316	1,031	-	-	
<1 unit a week	4,363	653	1.21	1.102,1.319		3,269	489	1.29	1.154,1.435		691	114	1.38	1.105,1.716	
>1 unit a week	163	23	1.13	0.722,1.754		126	14	0.78	0.436,1.395		NA	NA	NA	NA	
Inattentive	38,140	4,393			<0.001	28,512	3,186			<0.001	9,031	1,026			0.009
None (ref)	33,610	3,786	-	-		25,113	2,747	-	-		8,317	922	-	-	
<1 unit a week	4,367	584	1.22	1.106,1.337		3,273	426	1.28	1.142,1.440		691	103	1.46	1.162,1.833	
>1 unit a week	163	23	1.29	0.833,2.011		126	13	0.87	0.474,1.583		NA	NA	NA	NA	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals;*adjusted for child's gender, birth year, parity, maternal age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's alcohol consumption; NA – identifiability issue due to the low number of cases (<5 cases)*

Appendix 5.13. Associations between maternal alcohol consumption before pregnancy and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (RS-DBD)	41,020	5,455			<0.001	36,636	4,750			0.002	11,302	1,500			0.217
None (ref)	4,363	537	-	-		3,882	462	-	-		1,608	194	-	-	
<1 unit a week	15,062	1,825	0.98	0.886,1.089		13,551	1,595	1.01	0.901,1.133		3,808	487	1.09	0.877,1.348	
1-6 units a week	18,790	2,602	1.15	1.036,1.728		16,733	2,273	1.08	0.964,1.500		4,922	654	1.06	0.844,1.755	
>1 unit per day	2,805	491	1.51	1.322,1.805		2,470	420	1.28	1.099,1.805		964	165	1.31	0.981,1.805	
Hyperactive	41,011	5,381			<0.001	36,626	4,693			0.004	11,301	1,458			0.069
None (ref)	4,363	552	-	-		3,882	477	-	-		1,609	194	-	-	
<1 unit a week	15,059	1,768	0.92	0.828,1.018		13,548	1,552	0.94	0.840,1.053		3,808	464	1.03	0.829,1.279	
1-6 units a week	18,785	2,589	1.10	0.999,1.598		16,728	2,255	1.04	0.927,1.419		4,921	635	1.05	0.836,1.867	
>1 unit per day	2,804	472	1.40	1.222,1.805		2,468	409	1.22	1.040,1.805		963	165	1.39	1.041,1.805	
Inattentive	41,029	4,775			<0.001	36,642	4,169			0.115	11,302	1,307			0.629
None (ref)	4,363	476	-	-		3,881	415	-	-		1,607	171	-	-	
<1 unit a week	15,065	1,604	0.97	0.873,1.085		13,554	1,407	0.99	0.875,1.111		3,808	421	1.09	0.866,1.376	
1-6 units a week	18,790	2,288	1.13	1.019,1.594		16,731	2,001	1.05	0.929,1.180		4,922	591	1.11	0.869,1.472	
>1 unit per day	2,811	407	1.38	1.199,1.805		2,476	346	1.22	1.040,1.805		965	124	1.07	0.783,1.805	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals;*adjusted for child's gender, birth year, parity, maternal age, education, marital status, financial difficulties, depression and anxiety symptoms, smoking and caffeine consumption before pregnancy; **additionally adjusted for partner's alcohol consumption before partner's pregnancy*

Appendix 5.14. Associations between maternal alcohol consumption before pregnancy and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (DAWBA)	7,722	1,117			0.177	6,639	931			0.087	5,410	738			0.002
None (ref)	483	91	-	-		397	67	-	-		297	46	-	-	
<1 unit a week	2,897	385	0.66	0.513,0.849		2,484	317	0.76	0.562,1.024		2,027	249	0.87	0.603,1.260	
1-6 units a week	3,446	471	0.68	0.532,0.874		3,012	413	0.85	0.629,1.143		2,486	340	1.12	0.769,1.628	
>1 unit a week	896	170	1.01	0.760,1.338		746	134	1.08	0.764,1.525		600	103	1.45	0.937,2.243	
Hyperactive	7,743	984			0.664	6,656	824			0.632	5,420	645			0.023
None (ref)	485	86	-	-		398	65	-	-		298	41	-	-	
<1 unit a week	2,905	355	0.65	0.499,0.836		2,491	299	0.75	0.555,1.016		2,031	237	0.95	0.649,1.391	
1-6 units a week	3,454	404	0.62	0.476,0.793		3,018	347	0.76	0.558,1.023		2,490	280	1.07	0.727,1.587	
>1 unit a week	899	139	0.85	0.632,1.140		749	113	1.00	0.699,1.420		601	87	1.52	0.964,2.401	
Inattentive	7,734	1,060			0.213	6,653	885			0.168	5,418	714			0.004
None (ref)	484	85	-	-		397	63	-	-		297	45	-	-	
<1 unit a week	2,900	367	0.68	0.525,0.881		2,491	302	0.76	0.559,1.029		2,032	236	0.85	0.583,1.225	
1-6 units a week	3,459	450	0.70	0.544,0.905		3,023	393	0.82	0.603,1.106		2,492	331	1.08	0.740,1.576	
>1 unit a week	891	158	1.01	0.757,1.353		742	127	1.05	0.736,1.486		597	102	1.41	0.908,2.184	
ADHD (SDQ)	7,990	893			0.815	6,907	733			0.846	5,627	580			0.530
None (ref)	515	65	-	-		419	49	-	-		319	31	-	-	
<1 unit a week	2,987	343	0.90	0.677,1.192		2,588	286	1.03	0.737,1.433		2,115	234	1.34	0.878,2.031	
1-6 units a week	3,566	363	0.79	0.592,1.040		3,130	306	0.93	0.666,1.299		2,572	241	1.19	0.777,1.831	
>1 unit a week	922	122	1.06	0.765, 1457		770	92	1.09	0.738, 1.611		621	74	1.49	0.906, 2.439	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, maternal age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's alcohol consumption before pregnancy*

Appendix 5.15. Associations between maternal and paternal prenatal alcohol consumption and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (DAWBA)	5,736	806			0.353	4,584	576			0.753	3,565	420			0.941
None (ref)	2,572	350	-	-		2,044	256	-	-		1,615	184	-	-	
<1 unit a week	2,262	323	1.06	0.898,1.245		1,844	234	1.07	0.875,1.307		1,433	178	1.15	0.910,1.449	
>1 unit a week	902	133	1.10	0.885,1.362		696	86	0.89	0.675,1.182		517	58	0.90	0.638,1.259	
Hyperactive	5,735	725			0.053	4,584	520			0.261	3,565	376			0.228
None (ref)	2,572	313	-	-		2,044	225	-	-		1,615	160	-	-	
<1 unit a week	2,261	275	1.00	0.841,1.188		1,844	203	1.03	0.835,1.274		1,433	155	1.13	0.885,1.448	
>1 unit a week	902	137	1.29	1.041,1.606		696	92	1.18	0.890,1.553		517	61	1.16	0.824,1.630	
Inattentive	5,736	710			0.974	4,583	508			0.312	3,563	370			0.543
None (ref)	2,571	321	-	-		2,043	232	-	-		1,614	167	-	-	
<1 unit a week	2,263	274	0.97	0.813,1.147		1,844	205	1.02	0.829,1.259		1,432	154	1.07	0.842,1.370	
>1 unit a week	902	115	1.02	0.815,1.286		696	71	0.80	0.593,1.078		517	49	0.81	0.563,1.156	
ADHD (SDQ)	5,733	634			0.241	4,587	444			0.915	3,567	321			0.512
None (ref)	2,576	272	-	-		2,048	192	-	-		1,618	130	-	-	
<1 unit a week	2,255	255	1.08	0.901,1.294		1,843	190	1.21	0.965,1.507		1,432	147	1.37	1.053,1.776	
>1 unit a week	902	107	1.14	0.899,1.446		696	62	0.86	0.628,1.190		517	44	0.93	0.634,1.368	

Paternal															
ADHD (DAWBA)	4,212	538			0.103	3,075	334			0.854	3,067	334			0.787
None (ref)	155	22	-	-		84	11	-	-		84	11	-	-	
<1 unit a week	1,022	143	0.98	0.606,1.597		724	81	0.96	0.472,1.954		722	81	0.91	0.442,1.852	
1-6 units a week	2,231	280	0.87	0.543,1.386		1,661	181	1.07	0.537,2.136		1,658	181	1.00	0.499,2.019	
>1 unit a day	804	93	0.79	0.480,1.304		606	61	0.91	0.438,1.875		603	61	0.85	0.408,1.784	
Hyperactive	4,211	483			0.353	3,075	334			0.506	3,067	313			0.341
None (ref)	155	16	-	-		84	11	-	-		84	9	-	-	
<1 unit a week	1,022	129	1.26	0.725,2.174		724	81	1.20	0.556,2.569		722	81	1.13	0.526,2.447	
1-6 units a week	2,230	252	1.11	0.649,1.887		1,661	181	1.15	0.546,2.432		1,658	166	1.07	0.502,2.272	
>1 unit a day	804	86	1.04	0.592,1.828		606	61	1.00	0.456,2.183		603	57	0.91	0.409,2.000	
Inattentive	4,210	471			0.442	3,073	307			0.529	3,065	307			0.562
None (ref)	155	22	-	-		84	10	-	-		84	10	-	-	
<1 unit a week	1,022	124	0.84	0.512,1.361		724	76	1.01	0.485,2.085		722	76	0.95	0.457,1.986	
1-6 units a week	2,230	228	0.69	0.430,1.103		1,660	151	0.95	0.464,1.925		1,657	151	0.89	0.435,1.833	
>1 unit a day	803	97	0.83	0.505,1.367		605	70	1.16	0.552,2.421		602	70	1.10	0.520,2.329	
ADHD (SDQ)	4,209	416			0.190	3,079	261			0.991	3,071	261			0.793
None (ref)	155	18				84	9				84	9			
<1 unit a week	1,021	109	0.91	0.535,1.545		725	63	0.93	0.432,2.021		723	63	0.82	0.378,1.797	
1-6 units a week	2,227	215	0.81	0.488,1.356		1,662	137	0.99	0.469,2.097		1,659	137	0.86	0.401,1.836	
>1 unit a day	806	74	0.77	0.445,1.329		608	52	0.94	0.426,2.056		605	52	0.81	0.363,1.799	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's prenatal alcohol consumption*

Appendix 5.16. Associations between maternal prenatal weekly alcohol consumption in grams and high risk of maternal reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	n	OR	95% CI	P-value	N	n	OR	95% CI	P-value	N	n	OR	95% CI	P-value
ADHD (DAWBA)	7,180	1029	1.00	1.000,1.004	0.003	6,671	933	1.00	0.999,1.003	0.263	5,381	732	1.00	0.999,1.003	0.352
Hyperactive	7,200	911	1.00	1.000,1.004	0.007	6,689	828	1.00	0.999,1.003	0.170	5,391	642	1.00	0.999,1.004	0.240
Inattentive	7,192	987	1.00	1.001,1.004	0.004	6,684	889	1.00	0.999,1.003	0.168	5,389	707	1.00	0.999,1.004	0.126
ADHD (SDQ)	7,442	809	1.00	0.999,1.003	0.325	6,942	737	1.00	0.997,1.002	0.669	5,610	579	1.00	0.997,1.002	0.804

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's prenatal alcohol consumption*

Appendix 5.17. Associations between maternal prenatal weekly alcohol consumption in grams and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	n	OR	95% CI	P-value	N	n	OR	95% CI	P-value	N	n	OR	95% CI	P-value
ADHD (RS-DBD)	38,134	5,030	1.01	1.000,1.021	0.041	34,297	4,415	1.01	0.999,1.020	0.085	10,641	1,395	1.00	0.989,1.015	0.789
Hyperactive	38,127	4,957	1.01	0.999,1.019	0.074	34,290	4,353	1.01	0.996,1.015	0.231	10,638	1,351	1.00	0.985,1.014	0.969
Inattentive	38,140	4,393	1.01	1.001,1.021	0.038	34,302	3,874	1.01	0.999,1.019	0.091	10,639	1,210	1.00	0.987,1.015	0.920

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, maternal age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption before pregnancy; ** additionally adjusted for partner's alcohol consumption before partner's pregnancy*

Appendix 5.18. Associations between maternal and paternal prenatal alcohol consumption and high risk of maternal reported offspring ADHD symptoms in ALSPAC (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (DAWBA)	5,384	733			0.001			0.006			0.002
None (ref)	2,369	288	-	-		-	-		-	-	
<1 unit a week	2,220	311	1.18	0.991,1.398		1.30	1.002,1.432		1.23	1.026,1.471	
>1 unit a week	795	134	1.47	1.172,1.830		1.37	1.079,1.733		1.44	1.128,1.832	
Hyperactive	5,394	642			0.023			0.045			0.009
None (ref)	2,378	260	-	-		-	-		-	-	
<1 unit a week	2,221	272	1.14	0.949,1.362		1.16	0.961,1.394		1.20	0.991,1.443	
>1 unit a week	795	110	1.31	1.030,1.661		1.26	0.981,1.620		1.38	1.064,1.781	
Inattentive	5,392	708			0.001			0.007			0.004
None (ref)	2,375	279	-	-		-	-		-	-	
<1 unit a week	2,222	301	1.18	0.989,1.401		1.21	1.007,1.444		1.20	0.991,1.443	
>1 unit a week	795	128	1.44	1.149,1.808		1.37	1.075,1.736		1.38	1.064,1.781	
ADHD (SDQ)	5,613	579			0.004			0.020			0.008
None (ref)	2,471	222	-	-		-	-		-	-	
<1 unit a week	2,310	257	1.29	1.049,1.532		1.29	1.062,1.568		1.20	0.991,1.443	
>1 unit a week	832	100	1.38	1.077,1.778		1.30	0.997,1.684		1.38	1.064,1.781	

					Paternal					
ADHD (DAWBA)	4,648	622			0.096			0.204		0.048
None (ref)	148	36	-	-		-	-		-	-
<1 unit a week	1,053	136	0.46	0.304,0.700		0.49	0.314,0.749		0.45	0.292,0.701
1-6 units a week	2,465	320	0.46	0.313,0.688		0.53	0.350,0.798		0.47	0.310,0.715
>1 unit a day	982	130	0.48	0.312,0.721		0.51	0.327,0.788		0.44	0.279,0.683
Hyperactive	4,657	535			0.003			0.018		0.004
None (ref)	148	30	-	-		-	-		-	-
<1 unit a week	1,059	131	0.56	0.357,0.863		0.61	0.384,0.954		0.56	0.350,0.905
1-6 units a week	2,470	275	0.49	0.324,0.750		0.58	0.376,0.898		0.54	0.343,0.855
>1 unit a day	980	99	0.44	0.281,0.694		0.50	0.312,0.798		0.47	0.288,0.771
Inattentive	4,657	614			0.253			0.363		0.102
None (ref)	148	32	-	-		-	-		-	-
<1 unit a week	1,056	141	0.56	0.364,0.858		0.59	0.379,0.923		0.51	0.320,0.796
1-6 units a week	2,467	304	0.51	0.338,0.767		0.56	0.368,0.862		0.45	0.291,0.699
>1 unit a day	986	137	0.59	0.380,0.900		0.62	0.397,0.975		0.49	0.308,0.781
ADHD (SDQ)	4,796	487			0.300			0.447		0.156
None (ref)	160	24	-	-		-	-		-	-
<1 glass a week	1,095	114	0.66	0.409,1.059		0.68	0.418,1.111		0.62	0.374,1.027
1-6 units a week	2,537	245	0.61	0.385,0.953		0.67	0.417,1.064		0.58	0.356,0.941
>1 unit a day	1,004	104	0.66	0.406,1.057		0.69	0.419,1.131		0.55	0.328,0.928

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption; **additionally adjusted for partner's prenatal alcohol consumption*

Appendix 5.19. Associations between maternal and paternal prenatal alcohol consumption and high risk of maternal and teacher reported offspring ADHD symptoms in GenR (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (CPRS-R)	1,532	196			0.292			0.353			0.581
None (ref)	630	72	-	-		-	-		-	-	
<1 unit a week	507	71	1.26	0.889,1.793		1.31	0.898,1.902		1.25	0.854,1.834	
>1 unit a week	395	53	1.20	0.822,1.755		1.20	0.788,1.831		1.12	0.720,1.735	
Hyperactive	1,533	144			0.285	-		0.284			0.164
None (ref)	631	66	-	-			-		-	-	
<1 unit a week	507	44	0.81	0.545,1.215		0.83	0.541,1.265		0.78	0.509,1.207	
>1 unit a week	395	34	0.81	0.522,1.245		0.78	0.483,1.257		0.71	0.433,1.169	
Inattentive	1,534	170			0.149	-	-	0.242	-	-	0.498
None (ref)	632	60	-	-							
<1 unit a week	507	62	1.33	0.912,1.934		1.35	0.909,2.016		1.28	0.851,1.913	
>1 unit a week	395	48	1.32	0.882,1.972		1.29	0.824,2.003		1.16	0.732,1.842	
ADHD (CBCL)	1,828	212			0.180	-	-	0.166	-	-	0.105
None (ref)	809	101	-	-							
<1 unit a week	574	67	0.93	0.667,1.288		0.98	0.685,1.400		0.94	0.651,1.356	
>1 unit a week	445	44	0.77	0.529,1.119		0.73	0.476,1.108		0.68	0.441,1.062	
ADHD (TRF)	1,148	126			0.059	-	-	0.267	-	-	0.178
None (ref)	539	72	-	-							
<1 unit a week	342	28	0.58	0.365,0.916		0.64	0.387,1.068		0.60	0.357,1.013	
>1 unit a week	267	26	0.70	0.435,1.125		0.78	0.454,1.352		0.72	0.404,1.264	

						Paternal					
ADHD (CPRS-R)	1,937	261			0.188			0.114			0.163
None (ref)	201	19	-	-		-	-		-	-	
<1 unit a week	238	35	1.65	0.913,2.989		1.64	0.881,3.061		1.58	0.841,2.948	
1-6 units a week	982	133	1.50	0.904,2.491		1.64	0.940,2.855		1.56	0.880,2.746	
>1 unit a day	516	74	1.60	0.941,2.732		1.78	0.982,3.220		1.70	0.921,3.139	
Hyperactive	1,937	186			0.869			0.748			0.401
None (ref)	201	17	-	-		-	-		-	-	
<1 unit a week	238	31	1.62	0.869,3.025		1.62	0.835,3.130		1.68	0.866,3.270	
1-6 units a week	982	83	1.00	0.579,1.724		1.06	0.580,1.940		1.18	0.637,2.185	
>1 unit a day	516	55	1.29	0.730,2.284		1.35	0.709,2.567		1.57	0.808,3.045	
Inattentive	1,939	234			0.125			0.120			0.144
None (ref)	201	18	-	-		-	-		-	-	
<1 unit a week	238	31	1.52	0.824,2.813		1.42	0.743,2.693		1.38	0.719,2.629	
1-6 units a week	982	113	1.32	0.784,2.229		1.32	0.746,2.345		1.28	0.714,2.306	
>1 unit a day	518	72	1.64	0.952,2.829		1.66	0.907,3.049		1.63	0.869,3.045	
ADHD (CBCL)	2,332	278			0.158			0.637			0.865
None (ref)	299	39	-	-		-	-		-	-	
<1 unit a week	317	48	1.19	0.754,1.876		1.31	0.810,2.129		1.38	0.848,2.251	
1-6 units a week	1,139	126	0.83	0.565,1.218		0.98	0.633,1.504		1.09	0.699,1.710	
>1 unit a day	577	65	0.85	0.554,1.293		1.01	0.621,1.653		1.17	0.704,1.953	
ADHD (TRF)	1,452	149			0.247			0.977			0.680
None (ref)	213	28	-	-		-	-		-	-	
<1 unit a week	196	18	0.67	0.357,1.251		0.79	0.392,1.576		0.85	0.422,1.713	
1-6 units a week	695	70	0.74	0.463,1.182		0.98	0.565,1.713		1.15	0.643,2.039	
>1 unit a day	348	33	0.69	0.405,1.182		0.91	0.476,1.731		1.05	0.534,2.064	

*Note: CPRS-R – Revised Conners' Parent Rating Scale; CBCL – Child Behavior Checklist; TRF – Teacher Report Form; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals. *adjusted for child's gender, parity, parental ethnicity, age, education, anxiety and depression problems, financial difficulties, parental smoking and prenatal caffeine consumption in the maternal model. **additionally adjusted for partner's alcohol consumption*

Appendix 5.20. Associations between maternal and paternal prenatal alcohol consumption and high risk of maternal reported offspring ADHD symptoms in MoBa (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (RS-DBD)	10,641	1,395			<0.001			<0.001			<0.001
None (ref)	9,800	1,247	-	-		-	-		-	-	
<1 unit a week	811	146	1.51	1.246,1.820		1.53	1.258,1.857		1.53	1.260,1.865	
>1 unit a week	30	2	0.49	0.117,2.059		0.38	0.087,1.633		0.37	0.085,1.647	
Hyperactive	10,638	1,351			0.002			0.006			0.005
None (ref)	9,797	1,214	-	-		-	-		-	-	
<1 unit a week	811	133	1.39	1.138,1.690		1.38	1.129,1.690		1.40	1.139,1.710	
>1 unit a week	30	4	1.09	0.379,3.122		0.89	0.285,2.759		0.89	0.283,2.796	
Inattentive	10,639	1,210			0.003			0.003			0.002
None (ref)	9,799	1,087	-	-		-	-		-	-	
<1 unit a week	810	120	1.39	1.138,1.708		1.44	1.166,1.771		1.45	1.176,1.793	
>1 unit a week	30	3	0.89	0.270,2.941		0.74	0.202,2.730		0.74	0.197,2.777	

					Paternal					
ADHD (RS-DBD)	9,861	1,322			0.875			0.666		0.366
None (ref)	586	82	-	-		-	-	-	-	
<1 unit a week	2,945	403	0.97	0.753,1.261		1.00	0.761,1.301	0.97	0.742,1.270	
1-6 units a week	3,971	501	0.89	0.689,1.327		0.88	0.674,1.354	0.85	0.651,1.284	
>1 unit per day	2,359	336	1.02	0.786,1.509		1.02	0.773,1.509	0.97	0.731,1.509	
Hyperactive	9,858	1,294			0.929			0.950		0.616
None (ref)	586	86	-	-		-	-	-	-	
<1 unit a week	2,944	387	0.88	0.684,1.132		0.90	0.691,1.163	0.88	0.676,1.137	
1-6 units a week	3,969	490	0.82	0.640,1.226		0.82	0.632,1.268	0.79	0.611,1.206	
>1 unit per day	2,359	331	0.95	0.735,1.509		0.97	0.736,1.509	0.92	0.698,1.509	
Inattentive	9,862	1,129			0.971			0.524		0.293
None (ref)	586	72	-	-		-	-	-	-	
<1 unit a week	2,944	345	0.95	0.721,1.245		0.96	0.724,1.272	0.94	0.708,1.244	
1-6 units a week	3,972	423	0.85	0.651,1.314		0.83	0.628,1.303	0.81	0.607,1.238	
>1 unit per day	2,360	289	1.00	0.755,1.509		0.97	0.722,1.509	0.92	0.684,1.509	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal smoking and caffeine consumption. **additionally adjusted for partner's alcohol consumption*

Appendix 5.21. Associations between maternal alcohol consumption PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	1.41	0.197, 10.082	0.732	1.61	0.222, 11.715	0.636	2,022
Hyperactive	2.14	0.284, 16.174	0.460	2.44	0.316, 18.910	0.392	2,021
Inattentive	1.37	0.165, 11.347	0.772	1.67	0.197, 14.125	0.640	2,023
ADHD (SDQ)	2.22	0.259, 19.033	0.467	2.63	0.300, 22.989	0.383	2,018

Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Appendix 5.22. Associations between maternal daily prenatal caffeine consumption and high risk of maternal reported offspring ADHD symptoms in MoBa (adjusted for maternal ADHD)

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (RS-DBD)	42,206	5,607			0.002	28,507	3,655			0.025	10,649	1,441			0.099
0-49mg (ref)	26,564	3,506	-	-		18,128	2,294	-	-		6,695	880	-	-	
50-199mg	12,867	1,651	0.97	0.909,1.031		8,590	1,078	1.00	0.925,1.087		3,423	477	1.07	0.943,1.211	
200-299mg	1,869	282	1.17	1.024,1.334		1,206	175	1.15	0.964,1.368		387	55	1.05	0.767,1.424	
>300 mg	906	168	1.50	1.258,1.782		583	108	1.38	1.092,1.738		144	29	1.56	0.997,2.434	
Hyperactive	42,198	5,538			<0.001	28,504	3,600			<0.001	10,649	1,390			0.001
0-49mg (ref)	26,564	3,386	-	-		18,129	2,208	-	-		6,697	825	-	-	
50-199mg	12,861	1,701	1.04	0.980,1.111		8,586	1,102	1.08	0.993,1.166		3,421	480	1.18	1.038,1.334	
200-299mg	1,868	282	1.22	1.067,1.389		1,206	192	1.25	1.048,1.480		387	57	1.23	0.903,1.664	
>300 mg	905	169	1.57	1.322,1.869		583	108	1.42	1.127,1.788		144	28	1.71	1.093,2.660	
Inattentive	42,215	4,913			0.070	28,512	3,186			0.271	10,649	1,230			0.473
0-49mg (ref)	26,569	3,088	-	-		18,130	2,031	-	-		6,696	766	-	-	
50-199mg	12,872	1,443	0.96	0.898,1.026		8,594	916	0.97	0.886,1.052		3,423	394	1.01	0.882,1.154	
200-299mg	1,869	256	1.21	1.051,1.386		1,206	158	1.19	0.995,1.431		387	47	1.03	0.740,1.432	
>300 mg	905	126	1.23	1.014,1.492		582	81	1.15	0.895,1.489		143	23	1.39	0.868,2.215	

*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal smoking and alcohol consumption; **additionally adjusted for partner's caffeine consumption*

Appendix 5.23. Associations between maternal daily caffeine consumption before pregnancy and high risk of maternal reported offspring ADHD symptoms in MoBa

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
ADHD (RS-DBD)	42,206	5,607			0.057	36,636	4,750			0.373	13,573	1,819			0.276
0-49mg (ref)	17,079	2,297	-	-		14,480	1,905	-	-		5,105	672	-	-	
50-199mg	12,139	1,500	0.91	0.846,0.974		10,711	1,306	0.97	0.898,1.051		4,251	562	1.06	0.933,1.197	
200-299mg	6,351	836	0.98	0.896,1.062		5,606	703	0.99	0.898,1.091		2,198	300	1.11	0.948,1.290	
>300 mg	6,637	974	1.11	1.020,1.201		5,839	836	1.06	0.962,1.162		2,019	285	1.07	0.913,1.257	
Hyperactive	42,198	5,357			0.004	36,626	4,693			0.050	13,572	1,775			0.035
0-49mg (ref)	17,079	2,257	-	-		14,479	1,857	-	-		5,105	636	-	-	
50-199mg	12,136	1,452	0.89	0.831,0.958		10,707	1,264	0.96	0.890,1.042		4,250	557	1.11	0.982,1.264	
200-299mg	6,348	842	1.00	0.922,1.094		5,603	718	1.04	0.940,1.140		2,197	287	1.11	0.946,1.295	
>300 mg	6,635	986	1.15	1.056,1.244		5,837	854	1.10	1.004,1.211		2,020	295	1.18	1.008,1.385	
Inattentive	42,215	4,913			0.115	36,642	4,169			0.179	13,573	1,564			0.206
0-49mg (ref)	17,078	2,007	-	-		14,479	1,661	-	-		5,104	577	-	-	
50-199mg	12,148	1,320	0.92	0.850,0.986		10,717	1,159	1.00	0.924,1.091		4,254	477	1.05	0.918,1.200	
200-299mg	6,352	753	1.01	0.923,1.105		5,607	626	1.04	0.938,1.151		2,198	265	1.16	0.982,1.364	
>300 mg	6,637	833	1.08	0.988,1.176		5,839	723	1.07	0.971,1.186		2,017	245	1.08	0.915,1.286	

*Note: RS-DBD – Rating Scale of Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, maternal age, education, marital status, financial difficulties, depression and anxiety symptoms, smoking and alcohol consumption before pregnancy; **additionally adjusted for partner's caffeine consumption*

Appendix 5.24. Associations between maternal and paternal daily prenatal caffeine consumption and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Unadjusted model					Adjusted model*					Mutually adjusted model**				
	N	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**	**N**	**n**	**OR**	**95% CI**	**P-value**
								Maternal							
ADHD (DAWBA)	5,726	806			0.008	4,584	576			0.596	3,611	428			0.247
0-49mg (ref)	728	95	-	-		576	66	-	-		463	47	-	-	
50-199mg	2,259	293	0.99	0.775,1.273		1,855	215	1.08	0.793,1.462		1,483	155	1.08	0.752,1.537	
200-299mg	1,402	201	1.12	0.858,1.450		1,143	154	1.22	0.881,1.680		904	124	1.42	0.979,2.068	
>300mg	1,337	217	1.29	0.995,1.674		1,010	141	1.07	0.765,1.494		761	102	1.14	0.767,1.683	
Hyperactive	5,725	721			0.049	4,584	520			0.757	3,611	384			0.339
0-49mg (ref)	728	87	-	-		576	62	-	-		463	44	-	-	
50-199mg	2,259	265	0.98	0.756,1.267		1,855	194	1.00	0.731,1.370		1,483	143	1.05	0.728,1.523	
200-299mg	1,401	181	1.09	0.832,1.436		1,143	140	1.16	0.832,1.614		904	107	1.30	0.882,1.919	
>300mg	1,337	188	1.21	0.919,1.582		1,010	124	1.00	0.707,1.410		761	90	1.12	0.746,1.686	
Inattentive	5,726	710			0.014	4,583	508			0.874	3,609	374			0.610
0-49mg (ref)	727	79	-	-		575	56	-	-		462	38	-	-	
50-199mg	2,259	263	1.08	0.828,1.411		1,854	200	1.21	0.873,1.666		1,482	147	1.30	0.883,1.904	
200-299mg	1,402	181	1.22	0.918,1.610		1,143	133	1.24	0.879,1.746		904	104	1.44	0.959,2.156	
>300mg	1,338	187	1.33	1.007,1.763		1,011	119	1.09	0.765,1.560		761	85	1.16	0.761,1.779	
ADHD (SDQ)	5,723	633			0.014	4,587	444			0.830	3,613	328			0.309
0-49mg (ref)	727	74	-	-		577	52	-	-		464	35	-	-	
50-199mg	2,261	231	1.00	0.762,1.324		1,858	165	1.04	0.740,1.459		1,485	117	1.06	0.705,1.589	
200-299mg	1,400	155	1.10	0.820,1.472		1,142	116	1.13	0.790,1.623		904	94	1.37	0.894,2.084	
>300mg	1,335	173	1.31	0.984,1.753		1,010	111	1.02	0.706,1.483		760	82	1.14	0.730,1.768	

Paternal															
ADHD (DAWBA)	4,268	551			0.760	3,075	334			0.309	3,053	330			0.240
0-49mg (ref)	134	20	-	-		98	13	-	-		97	13	-	-	
50-199mg	511	64	0.82	0.474,1.404		367	39	0.87	0.430,1.746		366	38	0.81	0.403,1.638	
200-299mg	648	85	0.86	0.508,1.458		465	51	0.80	0.403,1.578		461	51	0.77	0.389,1.522	
>300mg	2,975	382	0.84	0.516,1.367		2,145	231	0.76	0.406,1.425		2,129	228	0.71	0.378,1.336	
Hyperactive	4,267	494			0.349	3,075	313			0.071	3,053	306			0.086
0-49mg (ref)	134	21	-	-		98	15	-	-		97	14	-	-	
50-199mg	511	57	0.68	0.393,1.161		367	39	0.76	0.386,1.482		366	38	0.78	0.390,1.546	
200-299mg	648	79	0.75	0.443,1.259		465	47	0.63	0.327,1.222		461	47	0.67	0.343,1.320	
>300mg	2,974	337	0.69	0.426,1.111		2,145	212	0.60	0.331,1.096		2,129	207	0.62	0.335,1.153	
Inattentive	4,266	480			0.289	3,073	307			0.937	3,051	303			0.942
0-49mg (ref)	134	17	-	-		98	12	-	-		97	12	-	-	
50-199mg	511	53	0.80	0.445,1.426		367	33	0.75	0.363,1.541		366	33	0.73	0.355,1.510	
200-299mg	647	58	0.68	0.381,1.205		464	37	0.58	0.284,1.184		460	37	0.57	0.280,1.168	
>300mg	2,974	352	0.92	0.549,1.555		2,144	225	0.77	0.407,1.469		2,128	221	0.75	0.391,1.422	
ADHD (SDQ)	4,265	426			0.425	3,079	261			0.679	3,057	258			0.483
0-49mg (ref)	134	15	-	-		98	11	-	-		97	11	-	-	
50-199mg	511	44	0.75	0.402,1.389		368	26	0.65	0.302,1.413		367	26	0.63	0.291,1.361	
200-299mg	647	61	0.83	0.454,1.502		466	39	0.68	0.326,1.429		462	39	0.66	0.314,1.374	
>300mg	2,973	306	0.91	0.525,1.577		2,147	185	0.69	0.353,1.361		2,131	182	0.64	0.325,1.265	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals. *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and alcohol consumption; **additionally adjusted for partner's prenatal caffeine consumption*

Appendix 5.25. Associations between maternal and paternal daily prenatal caffeine consumption and high risk of maternal reported offspring ADHD symptoms in ALSPAC (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (DAWBA)	5,447	745			0.002			0.131			0.191
0-49mg (ref)	735	84	-	-		-	-		-	-	
50-199mg	2,284	304	1.19	0.920,1.539		1.11	0.851,1.446		1.10	0.840,1.429	
200-299mg	1,354	175	1.15	0.872,1.518		1.04	0.784,1.390		1.02	0.767,1.365	
>300mg	1,074	182	1.58	1.198,2.087		1.29	0.965,1.732		1.26	0.937,1.695	
Hyperactive	5,458	653			0.021			0.299			0.381
0-49mg (ref)	735	74	-	-		-	-		-	-	
50-199mg	2,284	273	1.21	0.924,1.591		1.14	0.863,1.504		1.13	0.853,1.489	
200-299mg	1,359	152	1.13	0.839,1.509		1.04	0.769,1.405		1.02	0.755,1.384	
>300mg	1,080	154	1.49	1.106,1.995		1.25	0.919,1.702		1.22	0.896,1.673	
Inattentive	5,455	722			0.167			0.850			0.953
0-49mg (ref)	735	90	-	-		-	-		--	-	
50-199mg	2,292	302	1.09	0.846,1.399		1.01	0.781,1.310		1.00	0.769,1.293	
200-299mg	1,356	171	1.03	0.787,1.358		0.95	0.716,1.256		0.93	0.701,1.236	
>300mg	1,072	159	1.25	0.946,1.647		1.06	0.789,1.415		1.03	0.769,1.391	
ADHD (SDQ)	5,662	586			0.014			0.499			0.558
0-49mg (ref)	766	77	-	-		-	-		-	-	
50-199mg	2,349	229	0.97	0.736,1.269		0.91	0.693,1.206		0.91	0.691,1.206	
200-299mg	1,411	127	0.89	0.657,1.192		0.81	0.601,1.104		0.81	0.596,1.100	
>300mg	1,136	153	1.39	1.041,1.862		1.10	0.814,1.497		1.09	0.801,1.486	

Paternal										
ADHD (DAWBA)	4,625	617			0.473			0.874		0.786
0-49mg (ref)	151	18	-	-		-	-	-	-	
50-199mg	593	77	1.10	0.638,1.906		1.14	0.648,1.986	1.11	0.634,1.945	
200-299mg	729	94	1.09	0.639,1.873		1.07	0.616,1.853	1.02	0.588,1.773	
>300mg	3,152	428	1.16	0.702,1.919		1.11	0.661,1.853	1.03	0.615,1.734	
Hyperactive	4,634	533			0.568			0.750		0.976
0-49mg (ref)	150	18	-	-		-	-	-	-	
50-199mg	593	66	0.92	0.527,1.600		0.96	0.543,1.688	0.94	0.535,1.663	
200-299mg	732	76	0.85	0.492,1.468		0.85	0.485,1.482	0.82	0.469,1.438	
>300mg	3,159	373	0.98	0.593,1.626		0.98	0.583,1.640	0.93	0.554,1.567	
Inattentive	4,633	609			0.366			0.530		0.726
0-49mg (ref)	151	14	-	-		-	-	-	-	
50-199mg	597	78	1.47	0.808,2.678		1.55	0.839,2.845	1.52	0.827,2.805	
200-299mg	730	97	1.50	0.831,2.705		1.50	0.824,2.742	1.46	0.800,2.667	
>300mg	3,155	420	1.50	0.859,2.629		1.50	0.849,2.658	1.44	0.810,2.550	
ADHD (SDQ)	4,772	481			0.170			0.376		0.633
0-49mg (ref)	147	12	-	-		-	-	-	-	
50-199mg	612	58	1.18	0.615,2.255		1.28	0.664,2.481	1.26	0.650,2.432	
200-299mg	753	68	1.12	0.588,2.120		1.14	0.594,2.179	1.09	0.568,2.090	
>300mg	3,260	343	1.32	0.725,2.413		1.32	0.716,2.429	1.23	0.665,2.271	

*Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; N – total sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, ethnicity, parity, parental age, marital status, education, financial difficulties, depression and anxiety symptoms, prenatal smoking and alcohol consumption; **additionally adjusted for partner's prenatal caffeine consumption*

Appendix 5.26. Associations between maternal daily prenatal caffeine consumption and high risk of maternal and teacher reported offspring ADHD symptoms in GenR (complete cases)

			Unadjusted model			Adjusted model*		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
ADHD (CPRS-R)	2,053	282			0.733			0.438
0-49mg (ref)	383	62	-	-		-	-	
50-199mg	972	125	0.76	0.549,1.063		0.74	0.520,1.039	
200-299mg	357	43	0.71	0.466,1.078		0.71	0.456,1.106	
>300mg	341	52	0.93	0.624,1.392		0.83	0.534,1.297	
Hyperactive	2,057	201			0536			0.387
0-49mg (ref)	383	43	-	-		-	-	
50-199mg	976	94	0.84	0.575,1.235		0.85	0.572,1.266	
200-299mg	358	29	0.70	0.425,1.143		0.74	0.438,1.235	
>300mg	340	35	0.91	0.566,1.455		0.84	0.500,1.414	
Inattentive	2,058	240			0.978			0.701
0-49mg (ref)	383	53	-	-		-	-	
50-199mg	976	102	0.73	0.509,1.037		0.69	0.473,0.992	
200-299mg	358	40	0.78	0.505,1.214		0.77	0.483,1.214	
>300mg	341	45	0.95	0.618,1.451		0.84	0.526,1.342	
ADHD (CBCL)	2,565	331			0.760			0.285
0-49mg (ref)	490	64	-	-		-	-	
50-199mg	1,216	155	0.97	0.712,1.329		1.09	0.788,1.516	
200-299mg	445	54	0.92	0.624,1.354		1.12	0.742,1.690	
>300mg	414	58	1.08	0.740,1.589		1.26	0.824,1.923	
ADHD (TRF)	1,671	218			0.063			0.128
0-49mg (ref)	340	48	-	-		-	-	
50-199mg	777	112	1.03	0.711,1.476		1.17	0.791,1.734	
200-299mg	296	31	0.71	0.440,1.151		0.87	0.513,1.472	
>300mg	258	27	0.71	0.430,1.175		0.68	0.383,1.200	

*Note: CPRS-R–Revised Conners' Parent Rating Scale; CBCL–Child Behavior Checklist; TRF–Teacher Report Form; N–sample size; n–number. of cases; OR–odds ratio; 95% CI –95% confidence intervals; *adjusted for child's gender, parity, ethnicity, age, education, anxiety and depr. symptoms, fin. diff., smoking and alcohol use*

Appendix 5.27. Associations between maternal and paternal daily prenatal caffeine consumption and high risk of maternal reported offspring ADHD symptoms in MoBa (complete cases)

			Unadjusted model			Adjusted model*			Mutually adjusted model**		
	N	**n**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
					Maternal						
ADHD (RS-DBD)	12,621	1,686			0.030			0.053			0.045
0-49mg (ref)	7,844	1,021	-	-		-	-		-	-	
50-199mg	4,133	564	1.06	0.946,1.179		1.06	0.950,1.192		1.07	0.957,1.203	
200-299mg	473	66	1.08	0.829,1.417		1.08	0.815,1.425		1.09	0.820,1.435	
>300 mg	171	35	1.72	1.172,2.524		1.60	1.066,2.387		1.61	1.073,2.409	
Hyperactive	12,620	1,630			<0.001			<0.001			<0.001
0-49mg (ref)	7,845	956	-	-		-	-		-	-	
50-199mg	4,130	573	1.16	1.039,1.298		1.18	1.050,1.320		1.19	1.058,1.332	
200-299mg	474	65	1.15	0.871,1.506		1.15	0.867,1.532		1.17	0.878,1.550	
>300 mg	171	36	1.92	1.314,2.809		1.84	1.240,2.735		1.86	1.250,2.758	
Inattentive	12,620	1,448			0.156			0.228			0.249
0-49mg (ref)	7,845	888	-	-		-	-		-	-	
50-199mg	4,132	474	1.02	0.902,1.143		1.02	0.904,1.154		1.03	0.906,1.159	
200-299mg	473	58	1.10	0.824,1.454		1.09	0.810,1.463		1.09	0.807,1.459	
>300 mg	170	28	1.55	1.029,2.320		1.43	0.934,2.188		1.44	0.936,2.198	

					Paternal					
ADHD (RS-DBD)	10,804	1,462			0.968			0.535		0.710
0-49mg (ref)	2,353	344	-	-		-	-		-	-
50-199mg	3,861	478	0.83	0.711,0.958		0.85	0.731,0.999		0.84	0.720,0.985
200-299mg	3,231	448	0.94	0.808,1.094		0.99	0.838,1.157		0.97	0.820,1.136
>300 mg	1,359	192	0.96	0.794,1.162		1.01	0.824,1.227		0.98	0.804,1.199
Hyperactive	10,802	1,432			0.672			0.929		0.729
0-49mg (ref)	2,352	332	-	-		-	-		-	-
50-199mg	3,862	489	0.88	0.759,1.025		0.91	0.778,1.065		0.89	0.762,1.045
200-299mg	3,230	428	0.93	0.796,1.084		0.96	0.815,1.132		0.94	0.794,1.104
>300 mg	1,358	183	0.95	0.780,1.152		0.98	0.798,1.197		0.95	0.775,1.163
Inattentive	10,806	1,254			0.888			0.492		0.569
0-49mg (ref)	2,351	288	-	-		-	-		-	-
50-199mg	3,866	427	0.89	0.758,1.043		0.93	0.785,1.096		0.92	0.777,1.086
200-299mg	3,230	368	0.92	0.781,1.086		0.97	0.816,1.158		0.96	0.804,1.143
>300 mg	1,359	171	1.03	0.842,1.262		1.09	0.877,1.342		1.07	0.862,1.322

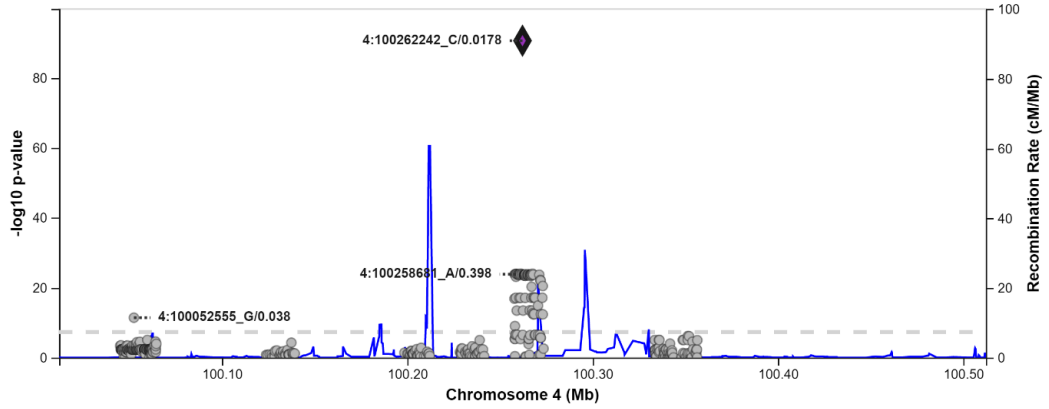
*Note: RS-DBD – Rating Scale for Disruptive Behavior Disorders; N – sample size; n – number of cases; OR – odds ratio; 95% CI – 95% confidence intervals; *adjusted for child's gender, birth year, parity, parental age, education, marital status, financial difficulties, depression and anxiety symptoms, prenatal smoking and alcohol consumption; **additionally adjusted for partner's caffeine consumption*

Appendix 5.28. Associations between maternal caffeine consumption PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Maternal PRS			Maternal PRS adj. for PC			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD (DAWBA)	0.68	0.355, 1.295	0.239	0.66	0.342, 1.253	0.201	3,486
Hyperactive	0.54	0.277, 1.060	0.074	0.52	0.268, 1.027	0.060	3,485
Inattentive	0.98	0.492, 1.951	0.954	0.95	0.476, 1.890	0.880	3,487
ADHD (SDQ)	0.59	0.287, 1.195	0.141	0.57	0.277, 1.155	0.118	3,486

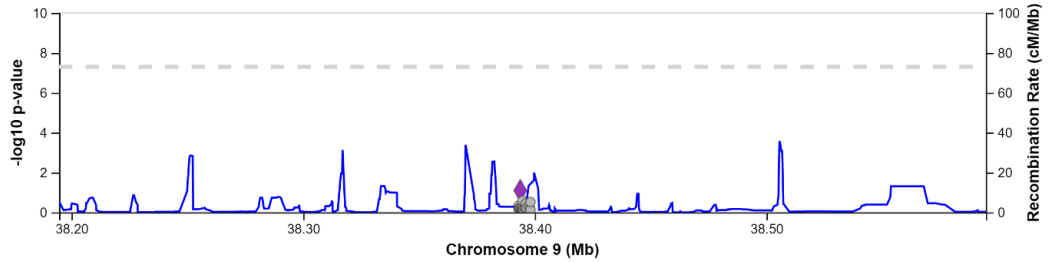
Note: DAWBA – Development And Well-Being Assessment; SDQ – Strengths and Difficulties Questionnaire; OR – odds ratio; 95% CI – 95% confidence intervals; PC – principal components

Appendix 6.1. SNPs positioned in chromosome 4 before clumping



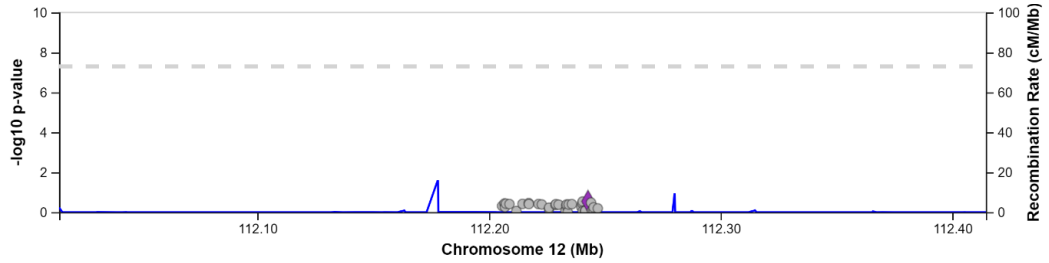
Note: 551 SNPs were identified from ADH4, ADH5, ADH6, ADH7, ADH1A, ADH1B, ADH1C genes

Appendix 6.2. SNPs positioned in chromosome 9 before clumping



Note: 280 SNPs were identified from ALDH1B1 and ALDH1A1 genes

Appendix 6.3. SNPs positioned in chromosome 12 before clumping



Note: 38 SNPs were identified from ALDH2 gene

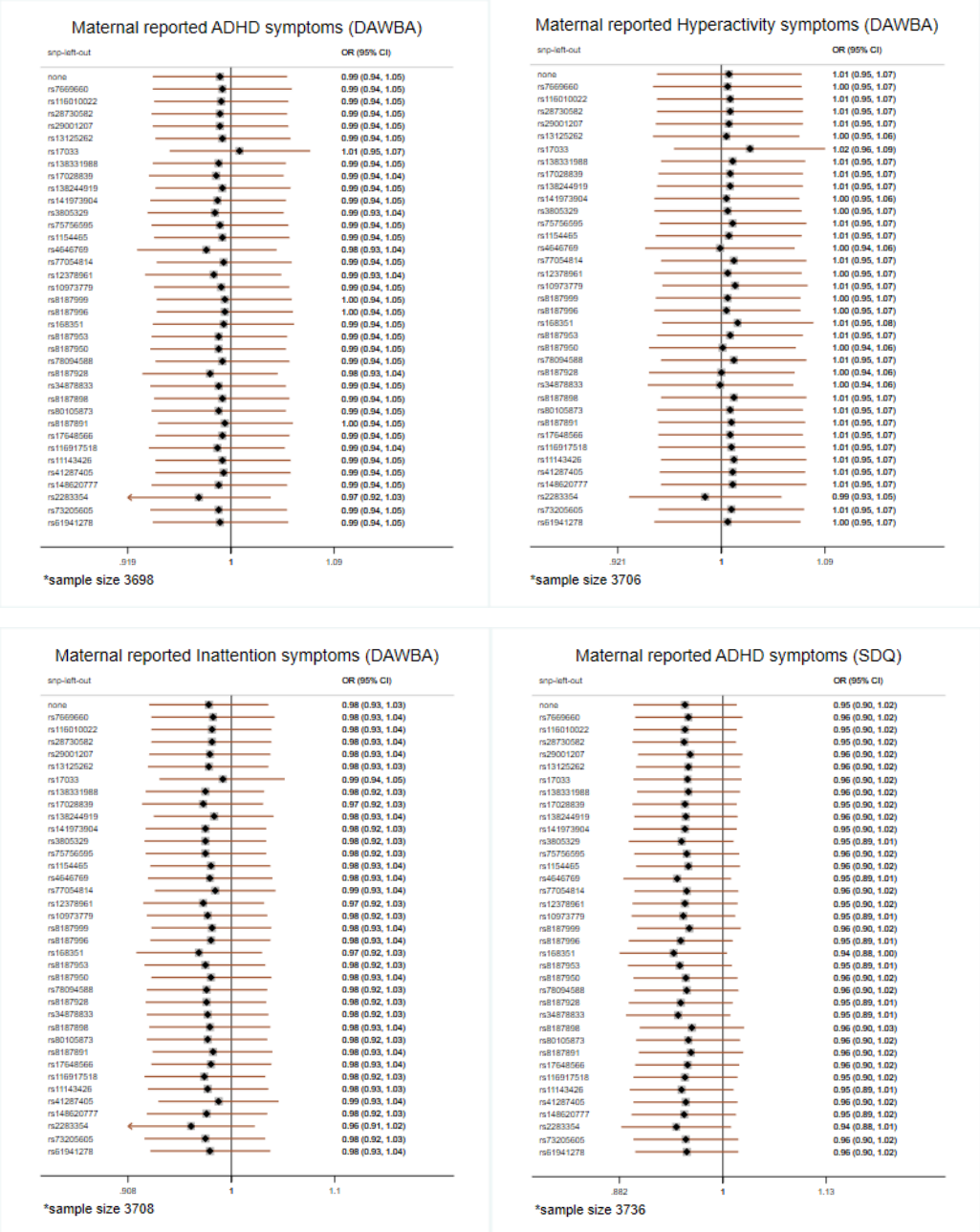
Appendix 6.4. Harmonisation of SNPs in GenR based on the GSCAN summary statistics

GSCAN					GenR			
SNP	**Non-effect allele**	**Effect allele**	**Effect allele frequency**	**Beta**	**Minor allele**	**Major allele**	**Major allele frequency**	**Effect allele after harmonisation**
rs7669660	T	C	0.136	0.0086	C	T	0.8480	C
rs116010022	C	A	0.00942	-0.0023	A	C	0.9921	C
rs28730582	C	T	0.0318	0.0149	T	C	0.9707	T
rs29001207	G	C	0.038	-0.0334	C	G	0.9554	G
rs13125262	G	C	0.0436	0.0160	C	G	0.9471	C
rs17033	T	C	0.0881	-0.0063	C	T	0.9137	T
rs138331988	G	A	0.0192	0.0042	A	G	0.9826	A
rs17028839	A	G	0.039	0.0031	G	A	0.9570	G
rs138244919	C	T	0.0272	0.0052	T	C	0.9821	T
rs141973904	C	T	0.0178	-0.1990	T	C	0.9809	C
rs3805329	T	C	0.0625	0.0105	C	T	0.9486	C
rs75756595	G	A	0.0522	0.0015	A	G	0.9599	A
rs1154465	T	A	0.0276	0.0061	A	T	0.9838	A
rs4646769	T	C	0.857	-0.0014	T	C	0.8085	T
rs77054814	A	G	0.067	0.0017	G	A	0.9521	G
rs12378961	C	G	0.0573	0.0068	G	C	0.9491	G
rs10973779	G	A	0.0299	-0.0067	A	G	0.9441	G
rs8187999	C	G	0.0238	0.0111	G	C	0.9740	G
rs8187996	C	T	0.0479	-0.0030	T	C	0.9525	C
rs168351	A	G	0.147	-0.0039	G	A	0.8714	A
rs8187953	C	G	0.0268	0.0011	G	C	0.9736	G
rs8187950	A	G	0.0364	-0.0033	G	A	0.9634	A
rs78094588	G	A	0.0233	0.0031	A	G	0.9793	A
rs8187928	C	T	0.0253	0.0103	T	C	0.9686	T
rs34878833	G	A	0.0231	0.0139	A	G	0.9708	A
rs8187898	T	C	0.0259	0.0038	C	T	0.9785	C

rs80105873	G	T	0.0289	-0.0029	T	G	0.9783	G
rs8187891	T	C	0.0252	0.0002	C	T	0.9781	C
rs17648566	T	C	0.0204	-0.0093	C	T	0.9747	T
rs116917518	A	T	0.0351	-0.0020	T	A	0.9596	A
rs11143426	A	G	0.0127	0.0147	G	A	0.9899	G
rs41287405	T	C	0.0238	0.0057	C	T	0.9729	C
rs148620777	A	G	0.0177	-0.0048	G	A	0.9839	A
rs2283354	G	A	0.174	0.0023	A	G	0.8045	A
rs73205605	G	A	0.036	-0.0018	A	G	0.9578	G
rs61941278	A	G	0.013	0.0075	G	A	0.9856	G

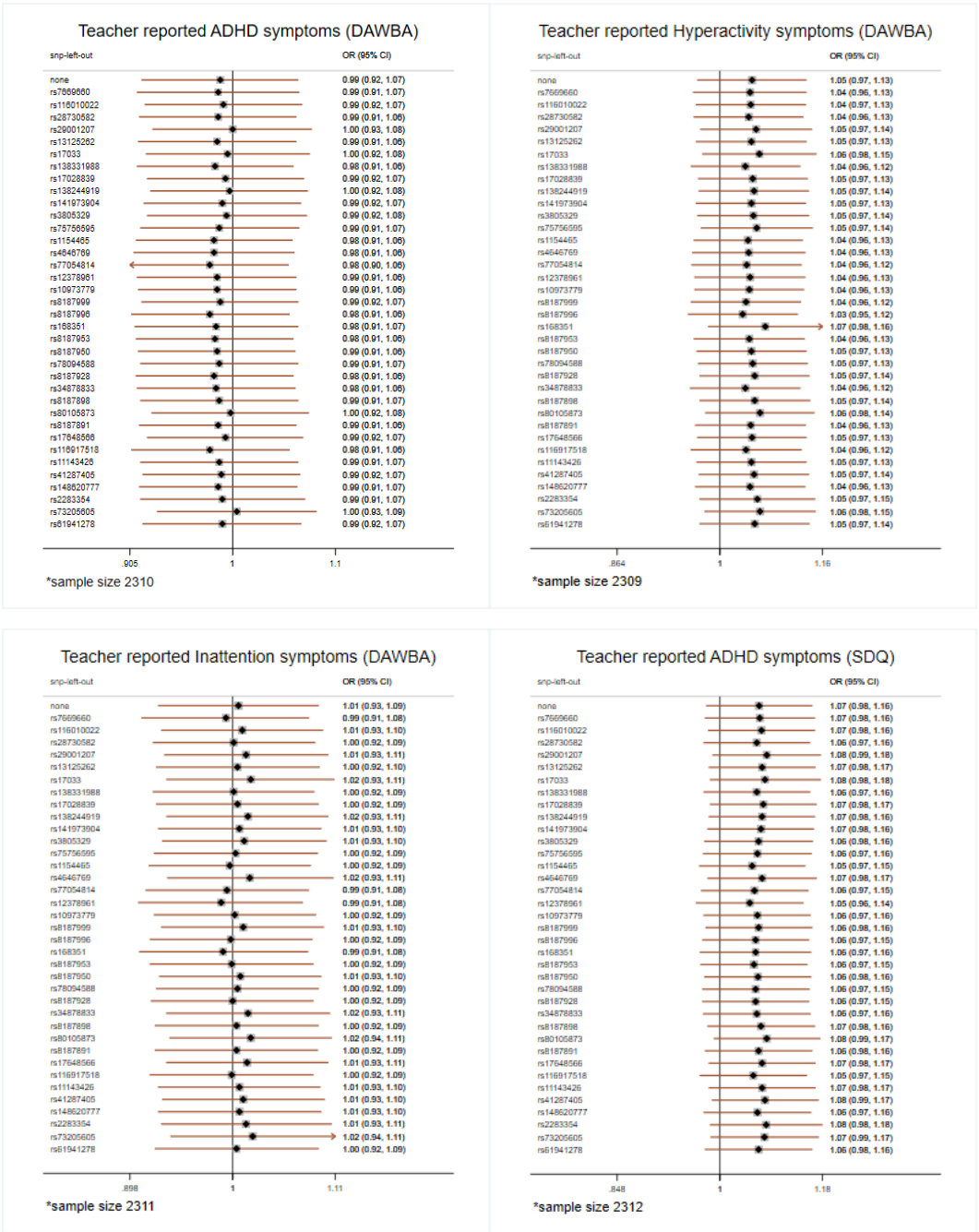
Note: GWAS & Sequencing Consortium of Alcohol and Nicotine use

Appendix 6.5. Leave-one-out analyses in ALSPAC between maternal PRS and high risk of maternal reported offspring ADHD symptoms



Note: Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.6. Leave-one-out analyses in ALSPAC between maternal PRS and high risk of teacher reported offspring ADHD symptoms

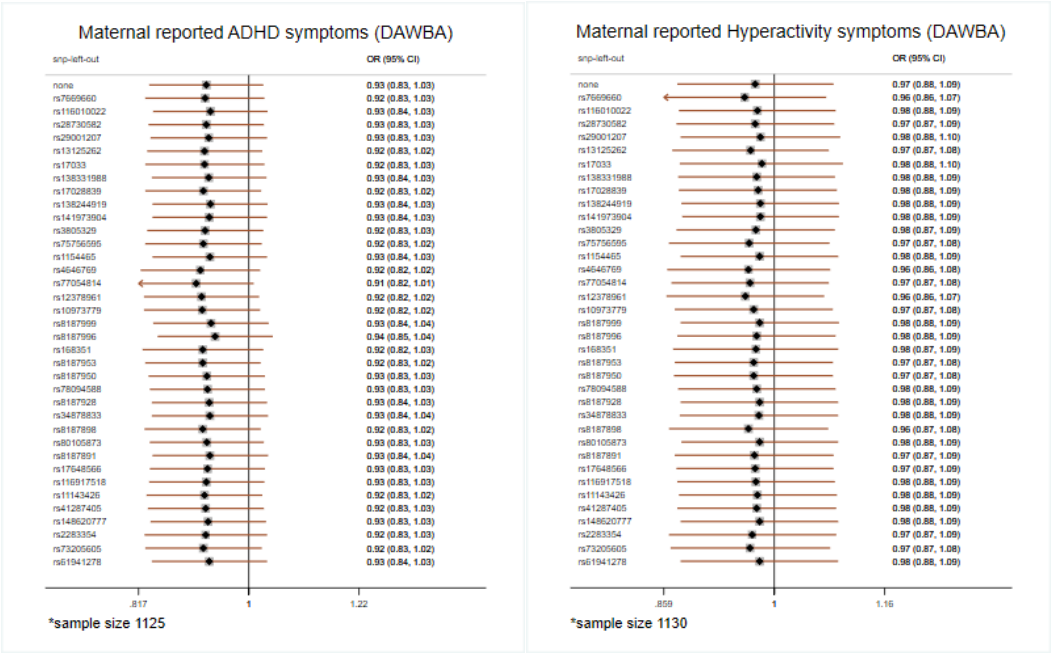


Note: Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.7. Leave-one-out analyses in ALSPAC between offspring PRS and high risk of maternal reported offspring ADHD symptoms if mother drank during pregnancy

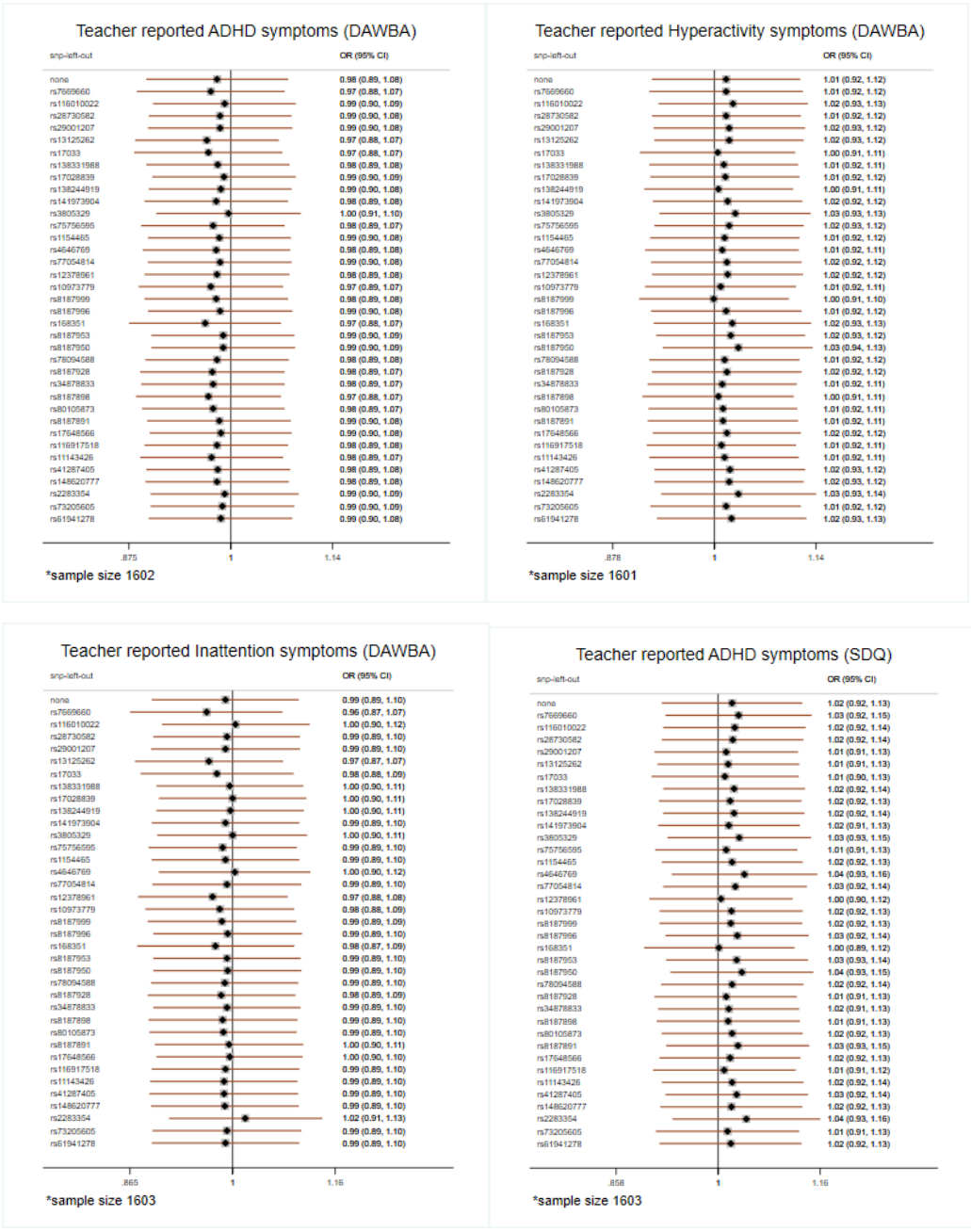
Note: Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.8. Leave-one-out analyses in ALSPAC between offspring PRS and high risk of maternal reported offspring ADHD symptoms if mother did not drink during pregnancy



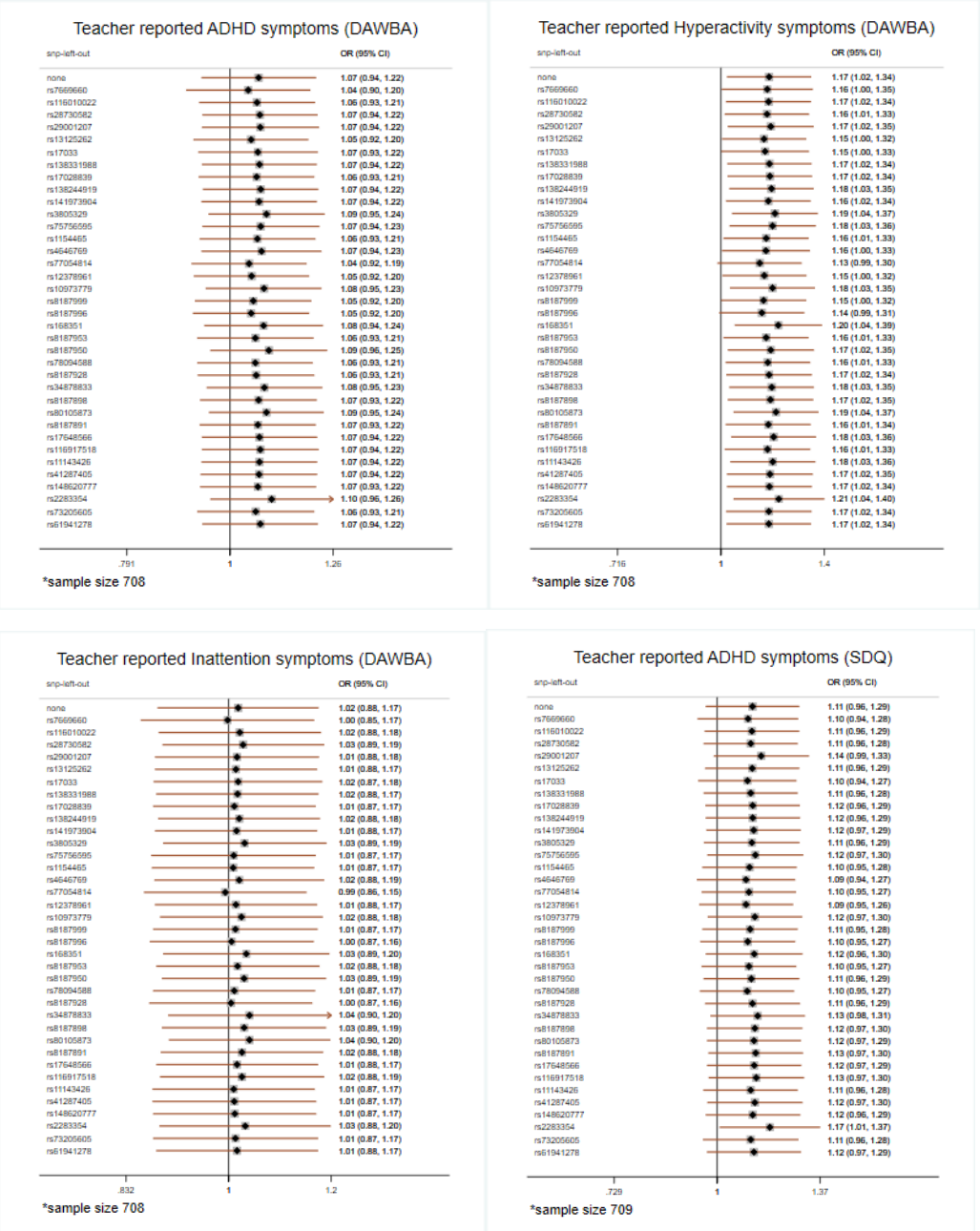
Note: Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.9. Leave-one-out analyses in ALSPAC between offspring PRS and high risk of teacher reported offspring ADHD symptoms if mother drank during pregnancy



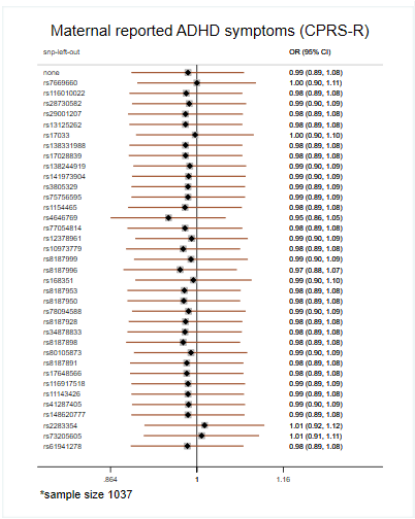
Note: Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

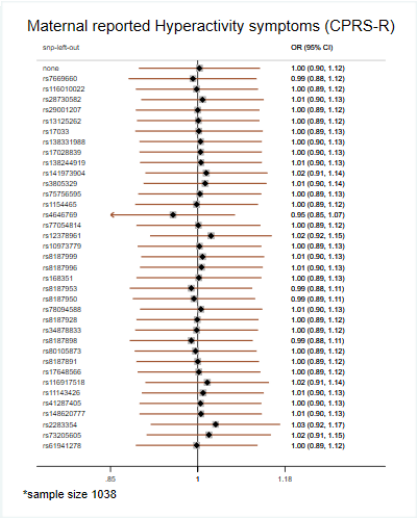
Appendix 6.10. Leave-one-out analyses in ALSPAC between offspring PRS and high risk of teacher reported offspring ADHD symptoms if mother did not drink during pregnancy

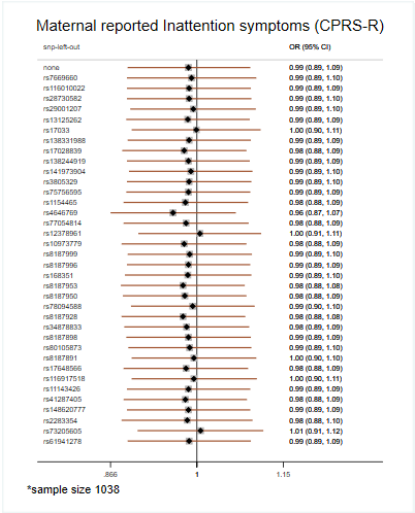


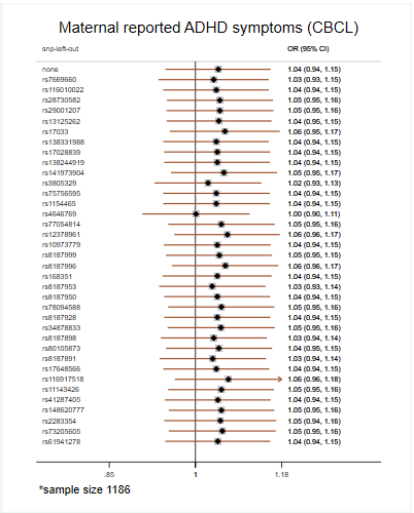
Note: Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

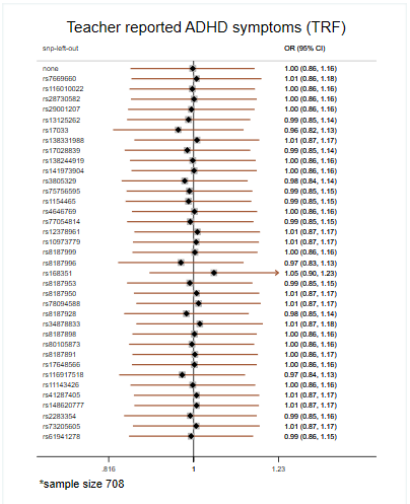
Appendix 6.11. Leave-one-out analyses in GenR between offspring PRS and high risk of maternal and teacher reported offspring ADHD symptoms if mother drank during pregnancy





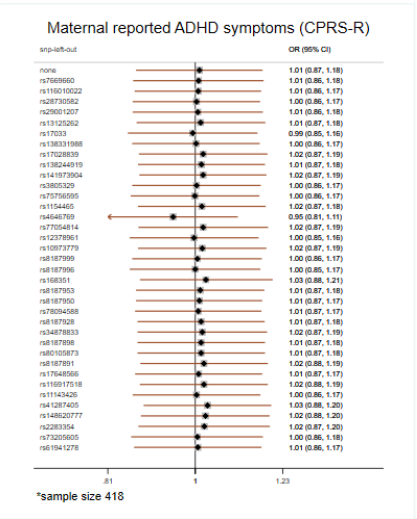


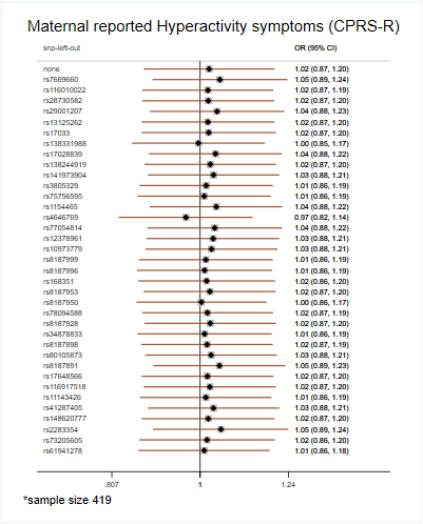


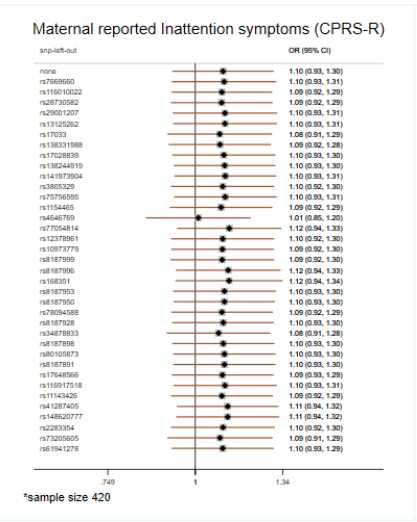


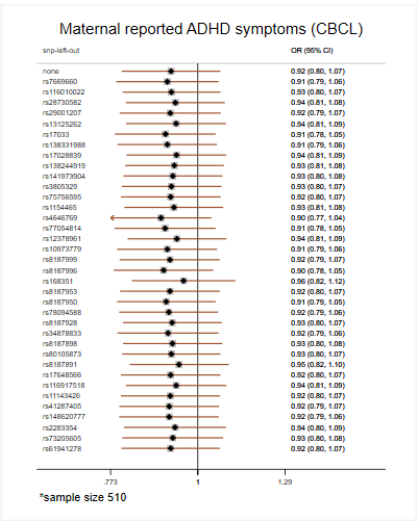
Note: Revised Conner's Parent Rating Scale (CPRS-R); Child Behavior Checklist (CBCL); Teacher Report Form (TRF)

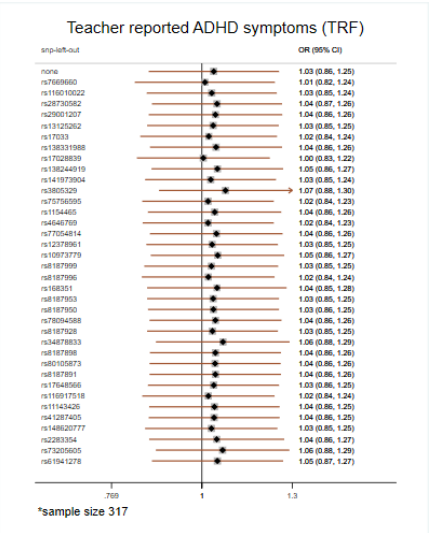
Appendix 6.12. Leave-one-out analyses in GenR between offspring PRS and high risk of maternal and teacher reported offspring ADHD symptoms if mother did not drink during pregnancy





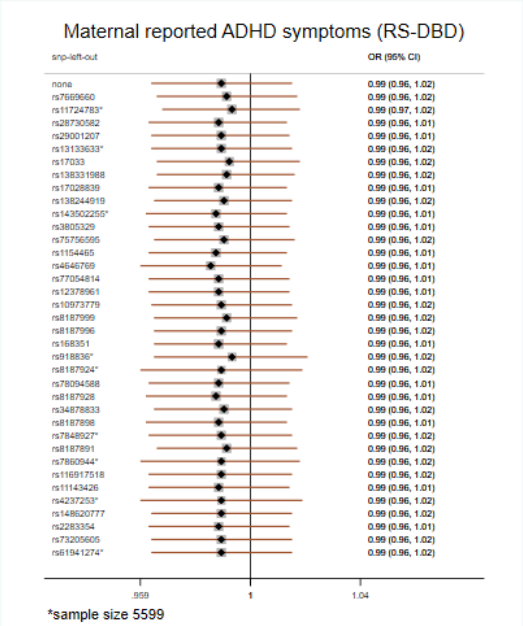


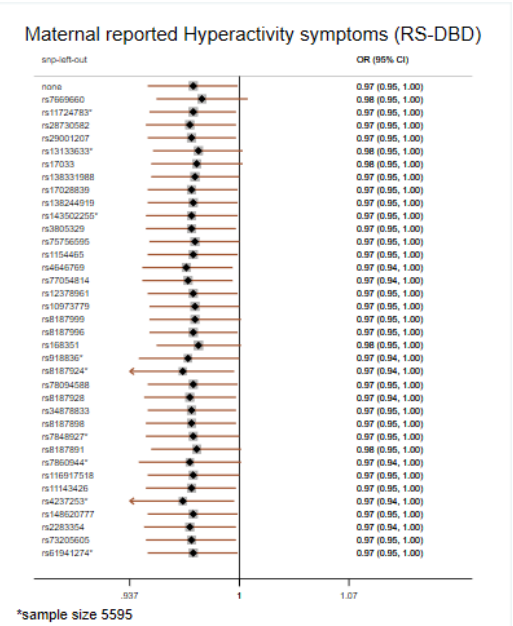


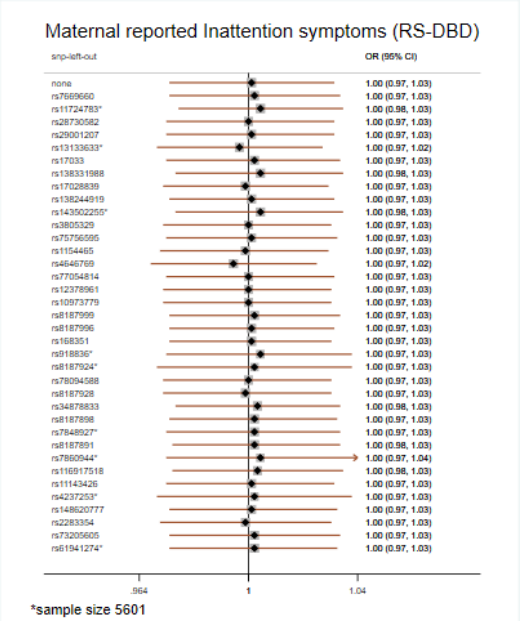


Note: Revised Conner's Parent Rating Scale (CPRS-R); Child Behavior Checklist (CBCL); Teacher Report Form (TRF)

Appendix 6.13. Leave-one-out analyses in MoBa between maternal PRS and maternal reported offspring ADHD symptoms

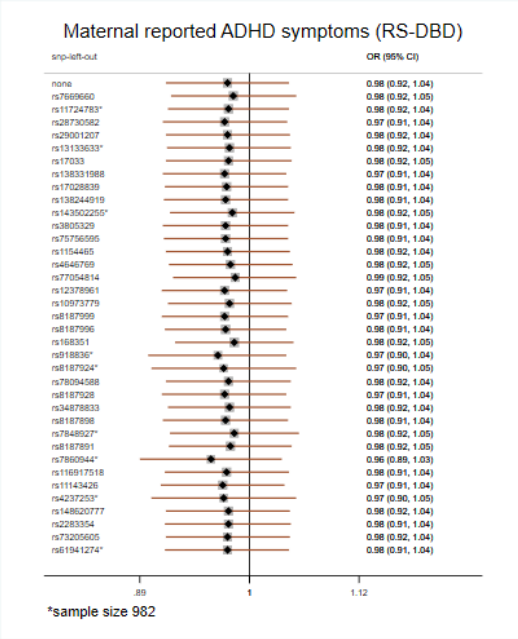


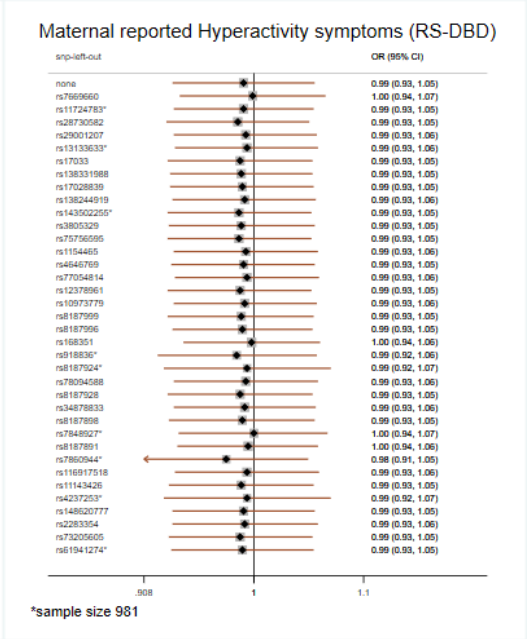


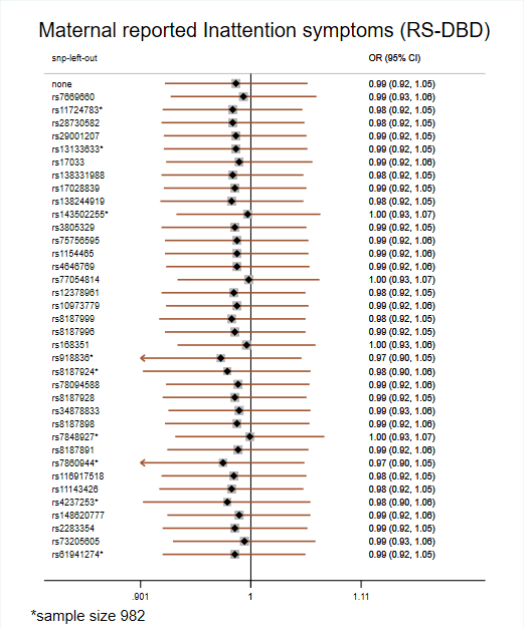


*Note: *new proxy SNP; Rating Scale for Disruptive Behavior Disorders (RS-DBD)*

Appendix 6.14. Leave-one-out analyses in MoBa between offspring PRS and high risk of maternal reported offspring ADHD symptoms if mother drank during pregnancy

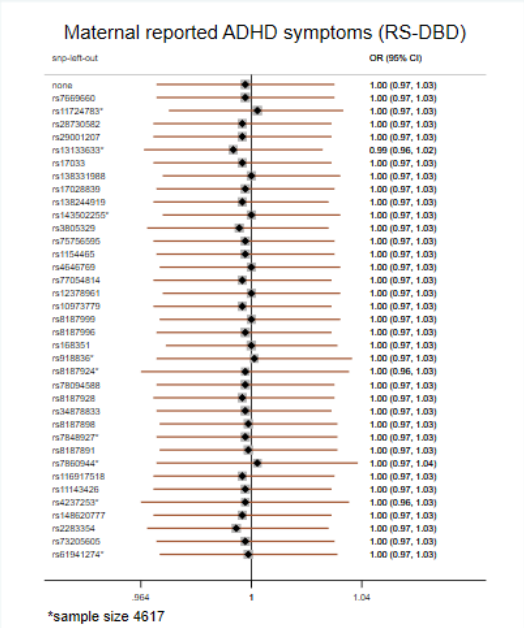


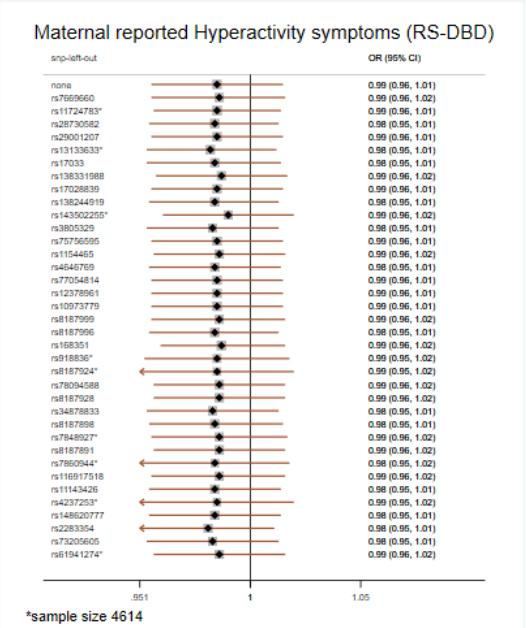


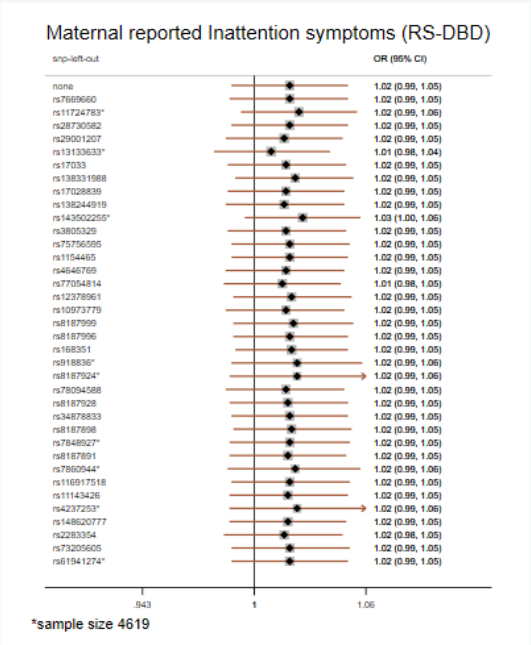


*Note: *new proxy SNP; Rating Scale for Disruptive Behavior Disorders (RS-DBD)*

Appendix 6.15. Leave-one-out analyses in MoBa between offspring PRS and high risk of maternal reported offspring ADHD symptoms if mother did not drink during pregnancy

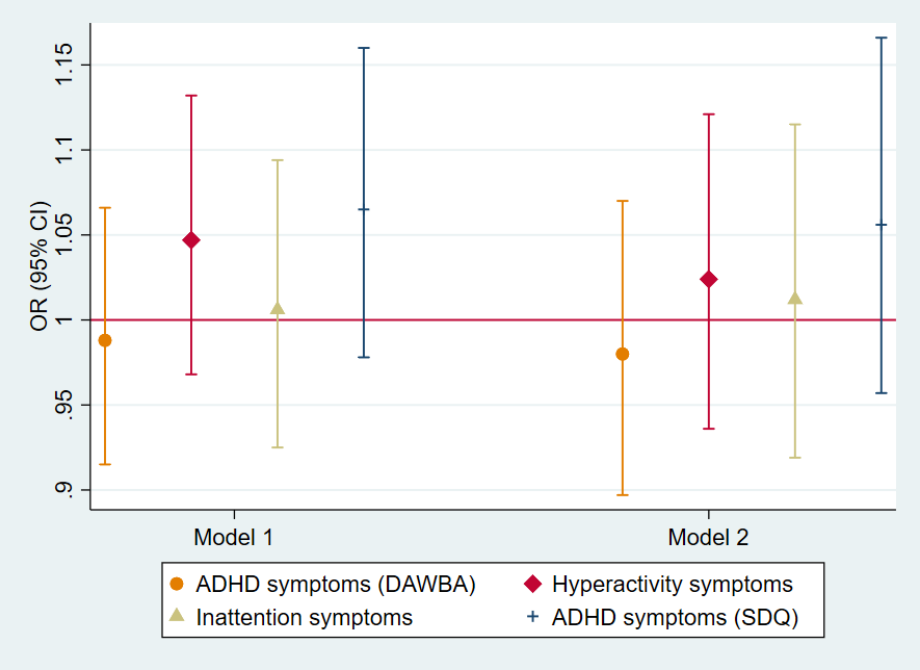






*Note: *new proxy SNP; Rating Scale for Disruptive Behavior Disorders (RS-DBD)*

Appendix 6.16. Associations between maternal PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC



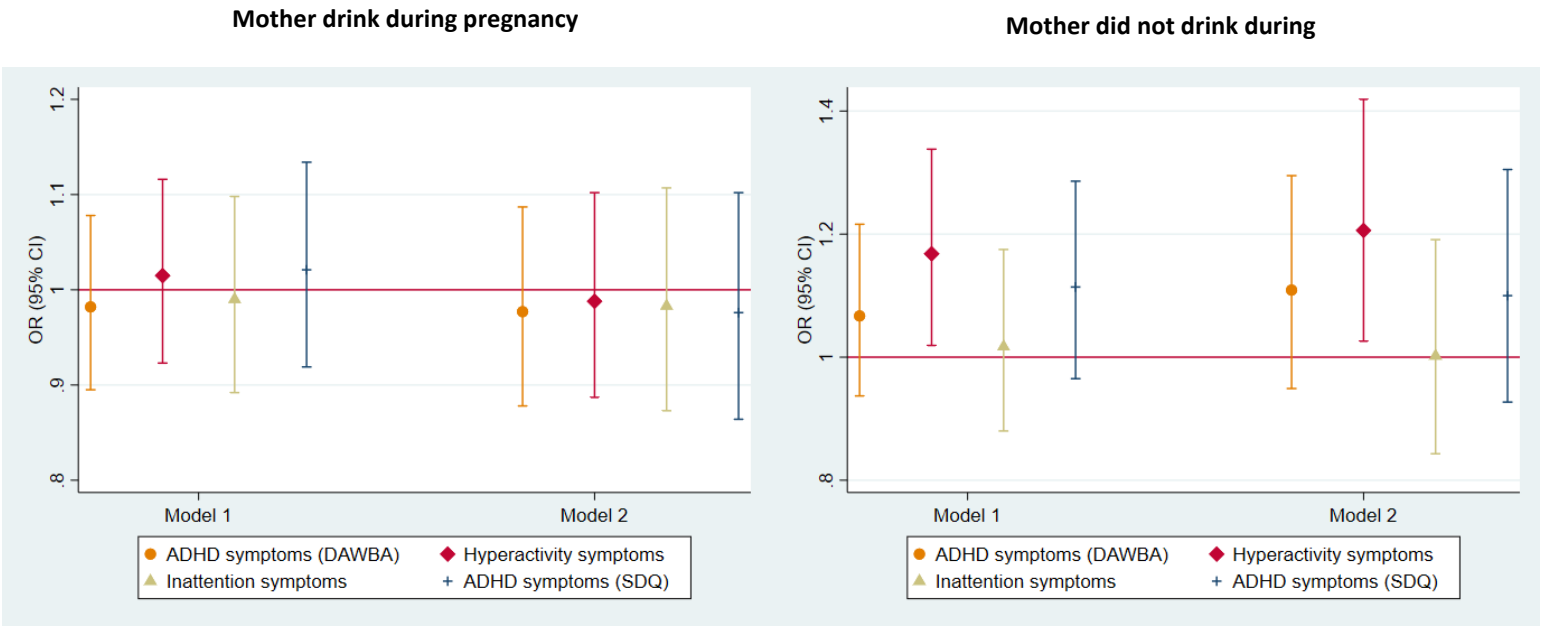
Note: Model 1 – only maternal PRS; Model 2 – maternal PRS adjusted for offspring PRS; All analyses are adjusted for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.17. Associations between maternal PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.99	0.915, 1.066	0.750	0.98	0.897, 1.070	0.649	2,310
Hyperactivity symptoms	1.05	0.968, 1.132	0.252	1.02	0.936, 1.121	0.599	2,309
Inattention symptoms	1.01	0.925, 1.094	0.889	1.01	0.919, 1.115	0.803	2,311
ADHD symptoms (SDQ)	1.07	0.978, 1.160	0.148	1.06	0.957, 1.166	0.277	2,312

Note: Model 1 – only maternal PRS; Model 2 – maternal PRS adj. for offspring PRS; All analyses adjusted also for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.18. Associations between offspring PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC stratified by maternal drinking status



Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adjusted for maternal PRS; All analyses are adjusted for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.19. Associations between offspring PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC if mother drank during pregnancy

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.98	0.895, 1.078	0.706	0.98	0.878, 1.087	0.666	1,602
Hyperactivity symptoms	1.02	0.923, 1.116	0.755	0.99	0.887, 1.102	0.832	1,601
Inattention symptoms	0.99	0.892, 1.098	0.843	0.98	0.873, 1.107	0.780	1,603
ADHD symptoms (SDQ)	1.02	0.919, 1.134	0.701	0.98	0.864, 1.102	0.691	1,603

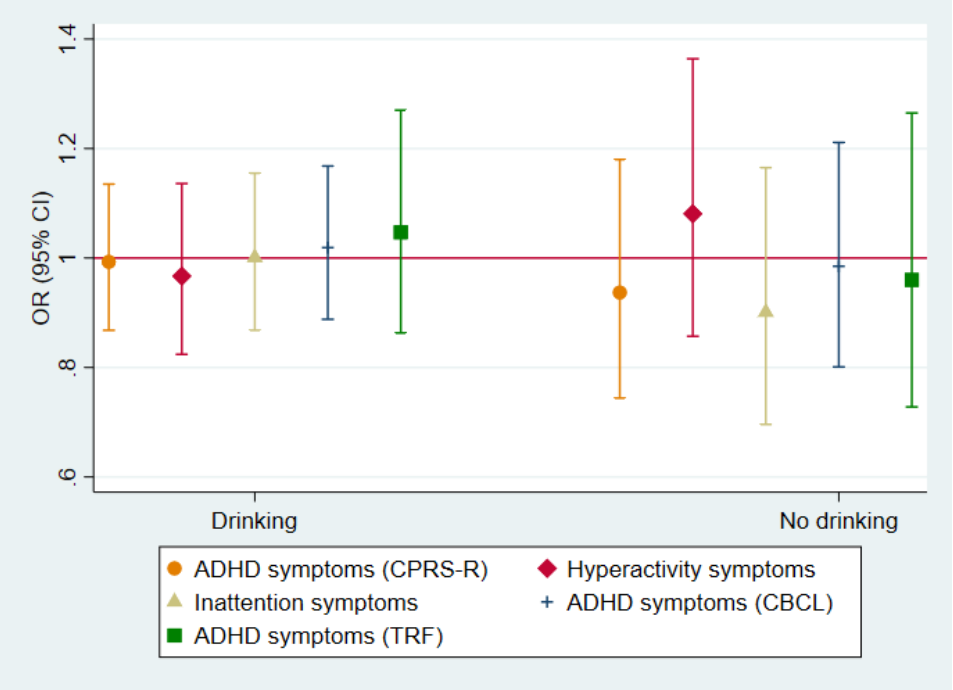
Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; All analyses adjusted also for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.20. Associations between offspring PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC if mother did not drink during pregnancy

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	1.07	0.937, 1.216	0.329	1.11	0.949, 1.295	0.192	708
Hyperactivity symptoms	1.17	1.019, 1.338	0.025	1.21	1.026, 1.419	0.023	708
Inattention symptoms	1.02	0.880, 1.175	0.822	1.00	0.843, 1.191	0.985	708
ADHD symptoms (SDQ)	1.11	0.965, 1.286	0.142	1.10	0.927, 1.305	0.277	709

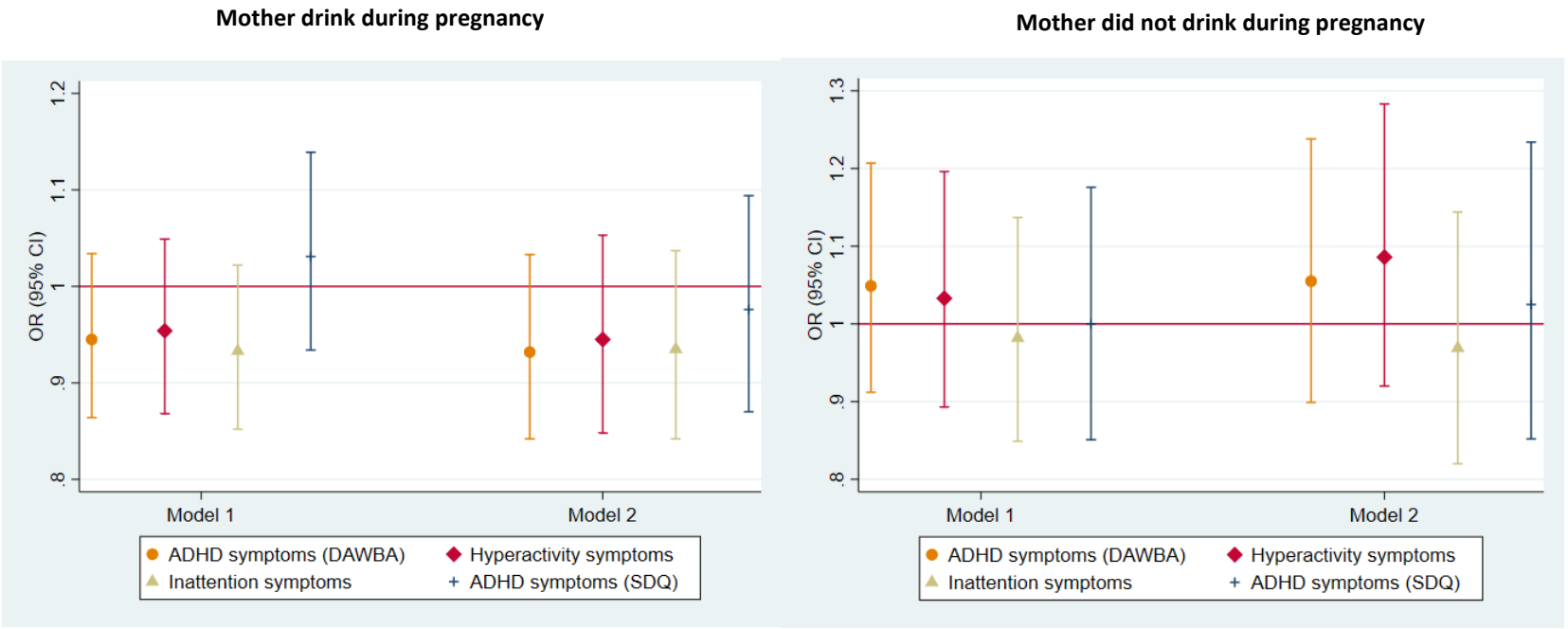
Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; All analyses adjusted also for 10 ancestry principal components; Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.21. Associations between offspring PRS and high risk of maternal and teacher reported offspring ADHD symptoms in GenR stratified by maternal drinking status



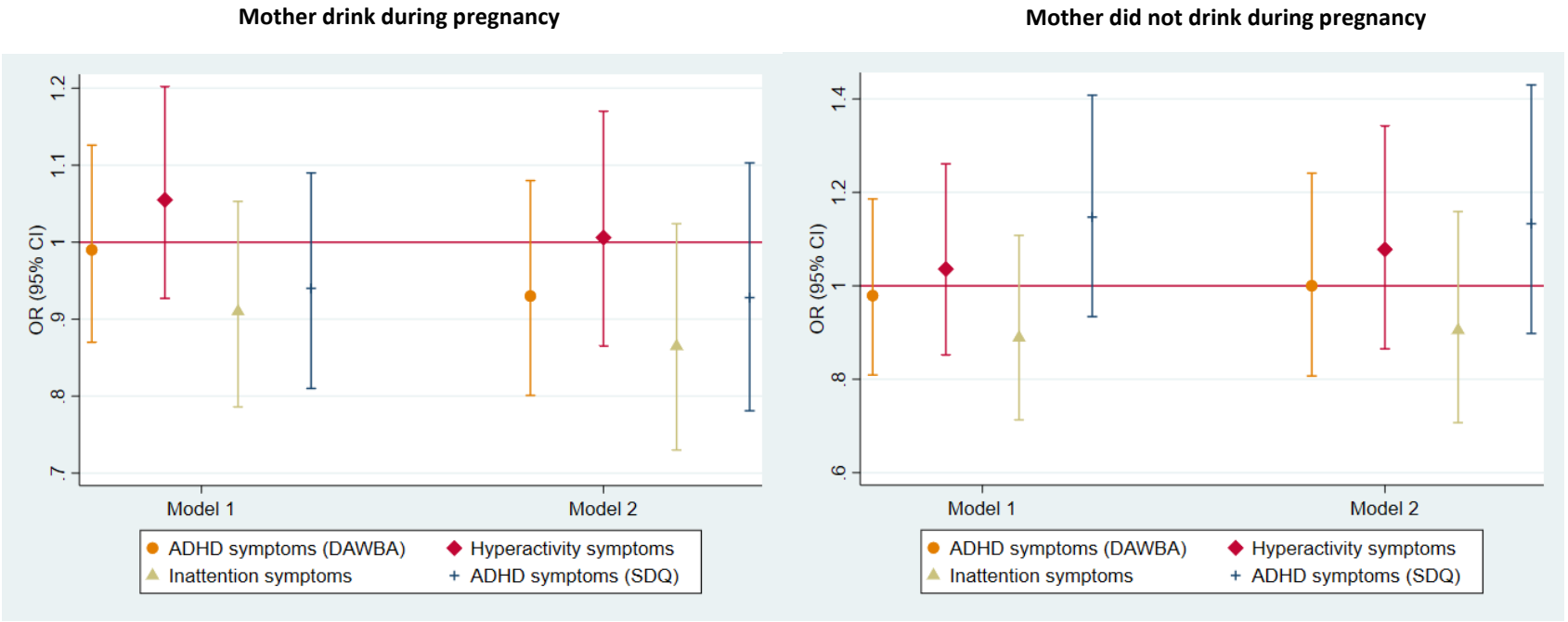
Note: Model 1 – only offspring PRS adjusted for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Revised Conner's Parent Rating Scale (CPRS-R); Child Behavior Checklist (CBCL); Teacher Report Form (TRF); CBCL and TRF are secondary measures

Appendix 6.22. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC stratified by maternal drinking status



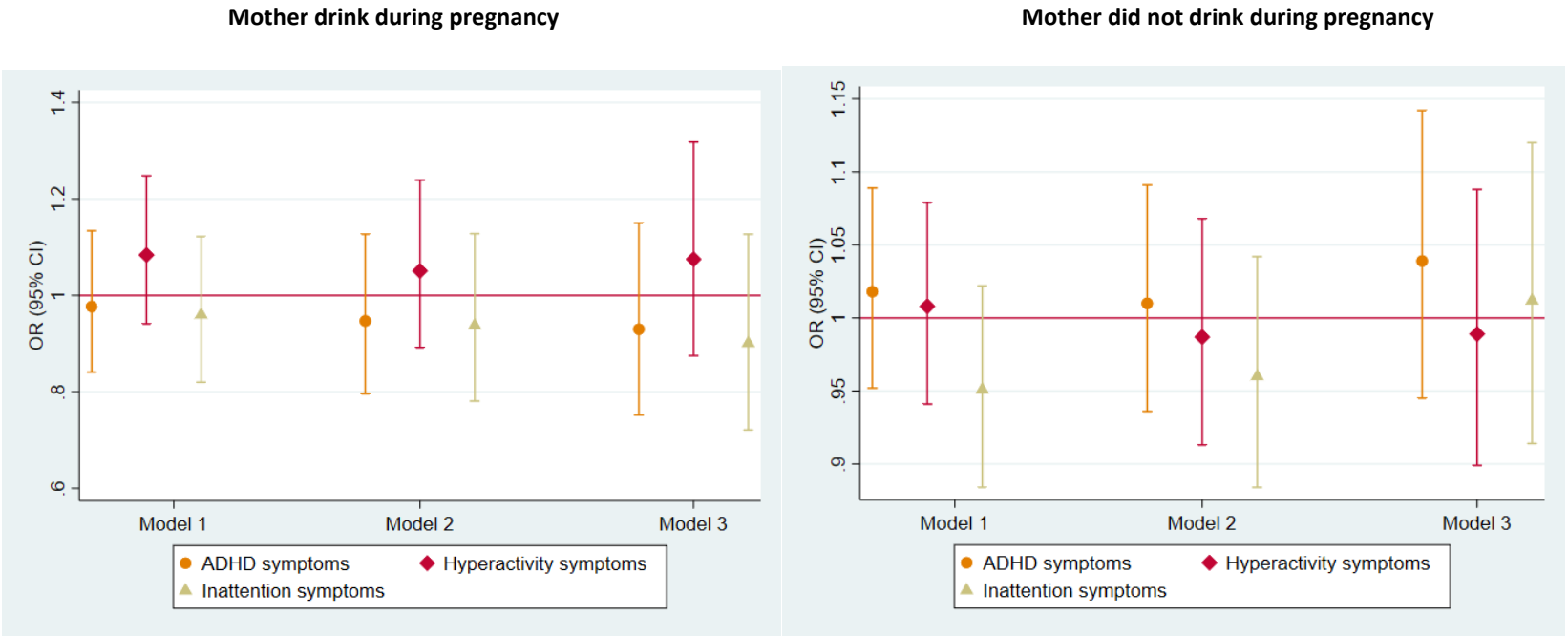
Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adjusted for maternal PRS; All analyses are adjusted for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Appendix 6.23. Associations between offspring PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC stratified by maternal drinking status



Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adjusted for maternal PRS; All analyses are adjusted for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Appendix 6.24. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in MoBa stratified by maternal drinking status



Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adjusted for maternal PRS; Model 3 – offspring PRS adjusted for maternal and paternal PRS; All analyses are adjusted for 10 ancestry principal components, birth year and genotyping batch; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); ADHD symptoms measured with Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Appendix 6.25. Associations between offspring PRS and high risk of maternal and teacher reported offspring ADHD symptoms in GenR

	Mother drink during pregnancy				Mother did not drink during pregnancy			
Outcome	**OR**	**95% CI**	**P-value**	**Sample size**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (CPRS-R)	0.99	0.868, 1.135	0.915	1,037	0.94	0.744, 1.180	0.581	418
Hyperactivity symptoms	0.97	0.824, 1.136	0.687	1,038	1.08	0.857, 1.364	0.512	419
Inattention symptoms	1.00	0.868, 1.155	0.990	1,038	0.90	0.696, 1.165	0.426	420
ADHD symptoms (CBCL)	1.02	0.888, 1.168	0.793	1,186	0.99	0.801, 1.211	0.884	510
ADHD symptoms (TRF)	1.05	0.863, 1.270	0.639	708	0.96	0.728, 1.265	0.770	317

Note: Model 1 – only offspring PRS adjusted also for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Revised Conner's Parent Rating Scale (CPRS-R); Child Behavior Checklist (CBCL); Teacher Report Form (TRF). CBCL and TRF are secondary measures

Appendix 6.26. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC if mother drank during pregnancy

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.95	0.864, 1.034	0.218	0.93	0.842, 1.033	0.181	2,573
Hyperactivity symptoms	0.95	0.868, 1.049	0.328	0.95	0.848, 1.053	0.307	2,576
Inattention symptoms	0.93	0.852, 1.022	0.134	0.94	0.842, 1.037	0.201	2,582
ADHD symptoms (SDQ)	1.03	0.934, 1.139	0.544	0.98	0.870, 1.094	0.672	2,606

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; All analyses adjusted also for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Appendix 6.27. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in ALSPAC if mother did not drink during pregnancy

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	1.05	0.912, 1.207	0.504	1.06	0.899, 1.238	0.514	1,125
Hyperactivity symptoms	1.03	0.893, 1.196	0.660	1.09	0.920, 1.283	0.330	1,130
Inattention symptoms	0.98	0.849, 1.137	0.808	0.97	0.820, 1.144	0.708	1,126
ADHD symptoms (SDQ)	1.00	0.851, 1.176	0.996	1.03	0.852, 1.234	0.790	1,130

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; All analyses adjusted also for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ) – secondary measure

Appendix 6.28. Associations between offspring PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC if mother drank during pregnancy

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.99	0.870, 1.126	0.876	0.93	0.801, 1.080	0.344	1,602
Hyperactivity symptoms	1.06	0.927, 1.202	0.416	1.01	0.865, 1.170	0.940	1,601
Inattention symptoms	0.91	0.786, 1.053	0.206	0.87	0.730, 1.024	0.092	1,603
ADHD symptoms (SDQ)	0.94	0.810, 1.090	0.413	0.93	0.781, 1.103	0.398	1,603

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; All analyses adjusted also for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.29. Associations between offspring PRS and high risk of teacher reported offspring ADHD symptoms in ALSPAC if mother did not drink during pregnancy

	Model 1			Model 2			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (DAWBA)	0.98	0.809, 1.186	0.830	1.00	0.807, 1.241	0.998	708
Hyperactivity symptoms	1.04	0.852, 1.261	0.723	1.08	0.865, 1.342	0.504	708
Inattention symptoms	0.89	0.713, 1.108	0.293	0.91	0.707, 1.159	0.429	708
ADHD symptoms (SDQ)	1.15	0.934, 1.408	0.191	1.13	0.898, 1.430	0.292	709

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; All analyses adjusted also for 10 ancestry principal components; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Development And Well-Being Assessment (DAWBA); Strengths and Difficulties Questionnaire (SDQ)

Appendix 6.30. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in MoBa if mother drank during pregnancy

	Model 1			Model 2			Model 3			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (RS-DBD)	0.98	0.841, 1.134	0.757	0.95	0.796, 1.127	0.538	0.93	0.752, 1.150	0.503	982
Hyperactivity symptoms	1.08	0.941, 1.248	0.263	1.05	0.892, 1.239	0.553	1.08	0.875, 1.318	0.494	981
Inattention symptoms	0.96	0.820, 1.122	0.606	0.94	0.781, 1.128	0.498	0.90	0.721, 1.127	0.362	982

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; Model 3 – offspring PRS adj. for maternal and paternal PRS; all analyses adjusted also for 10 ancestry principal components, birth year and genotyping batch; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Rating Scale for Disruptive Behavior Disorders (RS-DBD)

Appendix 6.31. Associations between offspring PRS and high risk of maternal reported offspring ADHD symptoms in MoBa if mother did not drink during pregnancy

	Model 1			Model 2			Model 3			
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**Sample size**
ADHD symptoms (RS-DBD)	1.02	0.952, 1.089	0.605	1.01	0.936, 1.091	0.793	1.04	0.945, 1.142	0.427	4,617
Hyperactivity symptoms	1.01	0.941, 1.079	0.823	0.99	0.913, 1.068	0.750	0.99	0.899, 1.088	0.821	4,614
Inattention symptoms	0.95	0.884, 1.022	0.168	0.96	0.884, 1.042	0.329	1.01	0.914, 1.120	0.820	4,619

Note: Model 1 – only offspring PRS; Model 2 – offspring PRS adj. for maternal PRS; Model 3 – offspring PRS adj. for maternal and paternal PRS; all analyses adjusted also for 10 ancestry principal components, birth year and genotyping batch; offspring PRS of 4 SNPs (rs2866151, rs975833, rs4147536, rs284779); Rating Scale for Disruptive Behavior Disorders (RS-DBD)